Explorations of Intramolecular [5+2] Cycloadditions of Ring-Constrained Vinylcyclopropanes

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Abstract

The first example of a [5+2] cycloaddition reaction wherein the olefin of the vinylcyclopropyl moiety is constrained in a carbocycle was explored, and possible reasons on the lack of reactivity of the substrate were studied. A simple model substrate was synthesized and subjected to cycloaddition conditions to determine if the reason for the lack of reactivity was related to the complexity of the substrate, or if the lack of "conjugative character" of the cyclopropyl ring with respect to the olefin is responsible. A more complex bicyclic substrate possessing an angular methyl group at the ring junction was also synthesized and explored, with evidence supporting the current theory of deconjugation of the cyclopropyl moiety.

Acknowledgements

First and foremost, I would like to extend my sincerest gratitude towards Professor Hudlicky for allowing me to rejoin his group as a graduate student. Despite working with the great Professor for over seven years now, it appears I still have many things to learn from him. I will undoubtedly look fondly upon my time in the Hudlicky research group for the rest of my life, and in all aspects of life I have become a better person for being a part of this wonderful community of budding chemists and creative scientists.

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Of course, to the rest of the Hudlicky group both past and present, you have my eternal gratitude. I've been a part of this group for such a long time, it'll be interesting to see how I adjust to life in the "real world" once again. Special thanks go to Sergey Vshyvenko, Vimal Varghese, Setu Gupta and Dave Adams, who were all essential to my success in one way or another, even if I didn't always realize it. Sergio Alatorre and John Trant are the kinds of chemists I one day aspire to become, and I'm honoured that I was able to work next to them. Thanks to Ales Machara for always putting things in perspective, and Ian Taschner for

reminding me that not everything in life needs to be such a big deal.

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List of Abbreviations

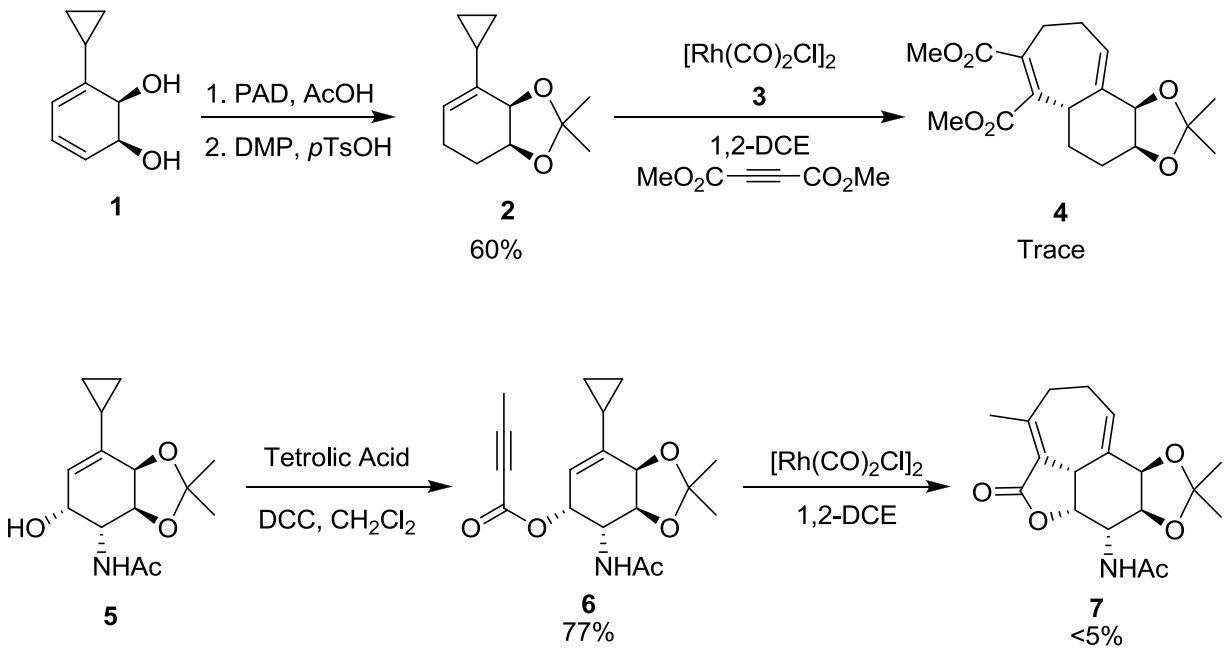
°C	Degrees Celsius
Ac	Acetyl
Bu	Butyl
Bn	Benzyl
Bz	Benzoyl
ca.	Circa
CAM	Ceric Ammonium Molybdate
CBz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
COD	Cyclooctadiene
d	Doublet
DCC	*N*,*N*`-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAD	Dimethyl but-2-ynedioate
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	2,2-Dimethoxypropane
Et	Ethyl
h	Hours
HBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium Hexafluorophosphate
hfacac	Hexafluoroacetoacetate
Hz	Hertz
IBX	1-hydroxy-1λ^5,2-benziodoxol-1,3-dione
IPA	*iso*-Propyl Alcohol
LAH	Lithium Aluminum Hydride
LG	Leaving Group
Ln	Ligand
*m*CPBA	*meta*-Chloroperbenzoic Acid
Me	Methyl
MEM	Methoxy Methyl
Min	Minutes
MS	Mass Spectrometry
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
PAD	Potassium Azodicarboxylate
PMP	*para*-Methoxyphenyl
Pr	Propyl
s	Singlet
t	Triplet
T3P	2,4,6-Tripropyl-1,3,5,2,4,6-Trioxatriphosphorinane-2,4,6-Trioxide
TBDMS	*tert*-Butyldimethylsilyl

TBS	*tert*-Butyldimethylsilyl
TDO	Toluene Dioxygenase
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TLC	Thin-layer Chromatography

1. Introduction

Cycloaddition reactions in general are extremely useful and atom-economical methods for the formation of ring structures, both hetero- and carbocyclic. While the literature contains many studies and reviews on the formation of five- and six-membered rings through the use of [3+2] and [4+2] cycloaddition reactions, there is comparatively less work on the analogous method for the formation of seven-membered rings.[1,2]

In 2011, Hudlicky and coworkers investigated the [5+2] cycloaddition between complex ring-constrained vinylcyclopropanes **2** and **6**.[3] The yields of both the inter- and intramolecular processes with these vinylcyclopropanes were surprisingly low, even after lengthy reaction times and high temperatures in sealed systems. The unexpected stability of these vinylcyclopropanes under these conditions was thought to be the result of the "non-conjugated" character of the cyclopropane with respect to the olefin.[3] In order to test this hypothesis, several model studies were undertaken on substrates in which the olefin of the vinylcyclopropane was constrained to a ring. The results of these model studies are reported in this dissertation.



Scheme 1 – Hudlicky's Ring-Constrained Vinylcyclopropane [5+2] Cycloadditions

2. Historical

2.1 – Cycloadditions Resulting in Seven-Membered Rings in Organic Synthesis

Seven-membered carbocycles are found in a large number of natural products, such as the frondosin family,[4] phorbol esters,[5] guanacasterpenes[6] and ingenol.[7] Strategies for the synthesis of such structural motifs are therefore wide-ranging, from metathesis reactions[8] and transition metal-catalyzed cyclizations[9] to cycloadditions.[10] Many of these reactions are performed as late-stage transformations, and are complicated by the active functionalities of other portions of the molecule; as such, the study of a general approach to these ubiquitous structural moieties is of the utmost importance.

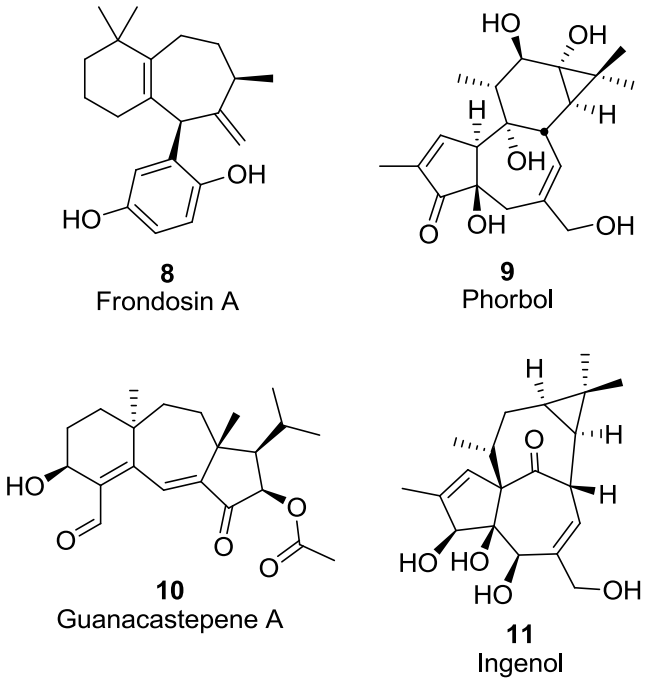
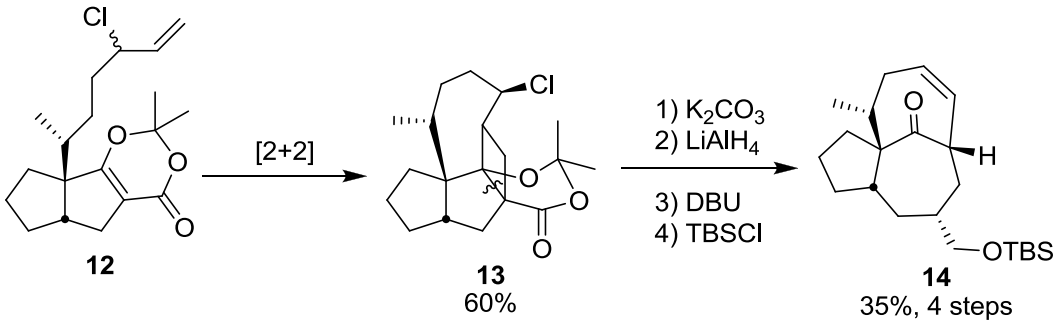
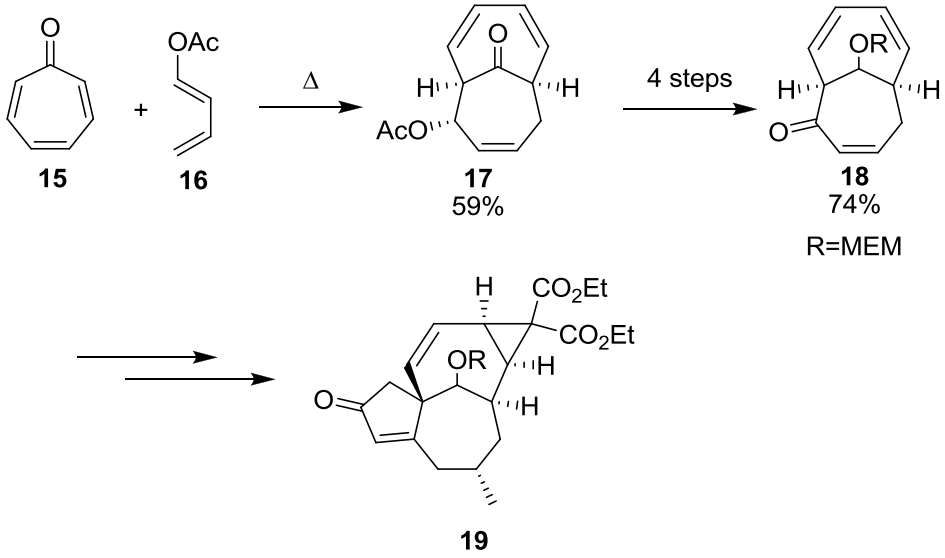


Figure 1 – Natural Products Containing Seven-Membered Rings

The synthesis of seven-membered rings is difficult to accomplish by direct cyclization methods, as the transition state of such reactions are generally destabilized by the presence of non-bonding interactions, and the reaction itself is unfavorable from an entropic standpoint.[11] These difficulties can be circumvented through the use of a cycloaddition reaction, most commonly a [4+3]- or [5+2]-cycloaddition. Seven-membered rings are also commonly formed utilizing a [2+2]-cycloaddition between two olefins, one of which is contained in a five-membered carbocycle. The resulting [3.2.0] framework can be fragmented, selectively breaking the internal bond to form a seven-membered ring, as exemplified by Winkler's 2002 synthesis of racemic ingenol **11**,[12] illustrated in **Scheme 2**. Winkler first synthesized the tricyclic system **12**, and using ultraviolet radiation was able to cyclize the vinyl chloride and olefin to provide cyclobutane **13**. This highly-strained system underwent base-mediated ring fragmentation along the indicated bond, and reduction, base-catalyzed isomerization and protection provided the tricyclic core of ingenol in four subsequent steps. Although the yield was not exceptional, the transformation did provide the correct stereochemistry at the newly-formed ring juncture. Previous attempts at the cyclization while utilizing a hydroxyl group in place of the chloride provided much lower yields, necessitating the use of the halide. The completion of the racemic synthesis required an additional 28 steps, however, as the unadorned core **14** was formed relatively early. The total step count was 43, with an average yield of 80% per step.



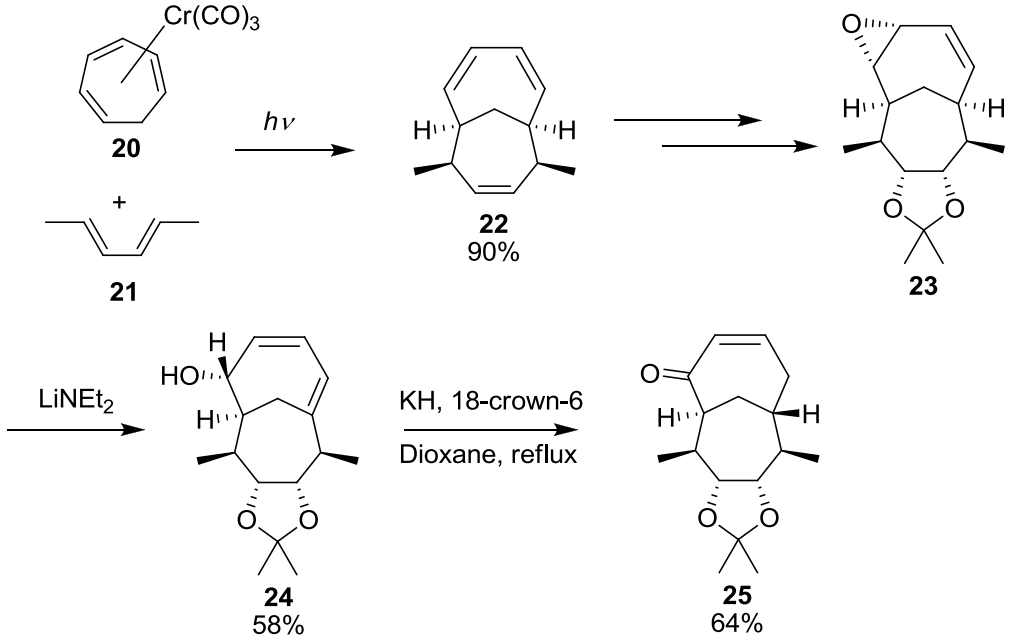
Scheme 2 – Winkler's Synthesis of Ingenol



Scheme 3 – Rigby's Approach Towards 8-Isoingenol

Another noteworthy approach to the ingenol core was completed by Rigby in 1993,[13] who utilized a [6π+4π] cycloaddition with tropone **15** to form the [4.4.1] core **17**, epimeric at C8. The cycloaddition was thermally driven, as opposed to Winkler's approach, although the yield was no better. The cycloaddition was the initial step in his synthesis, and provided a single diastereomer. Subsequent reduction of the ketone, protection with MEM-Cl, deprotection of the acetate and oxidation of the resulting

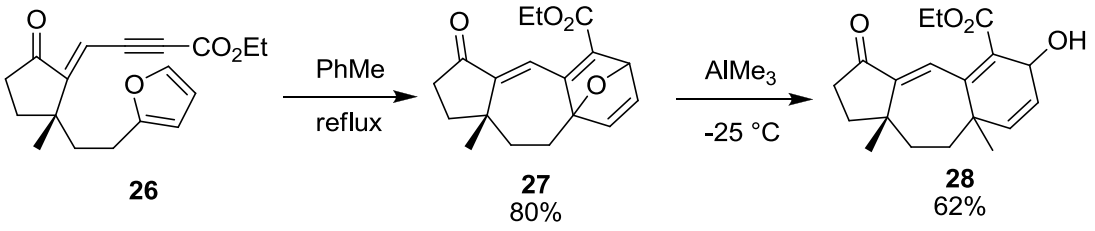
alcohol provided enone **18** in good yields as a mixture of diastereomers at C9, as indicated. In seven additional steps, Rigby was able to synthesize tricycle **19**, an advanced intermediate towards 8-isoingenol. In later studies,[14] he would go on to discover that the correct stereochemistry for natural ingenol could be obtained through an intramolecular (1,5)-hydride shift, and improved the yield on his initial cycloaddition drastically by creating a chromium complex with tropane, **20**, as shown in **Scheme 4**. The cycloaddition in this case required irradiation, but provided excellent yields and a single diastereomer.



Scheme 4 – Epimerization at C8 Towards Ingenol

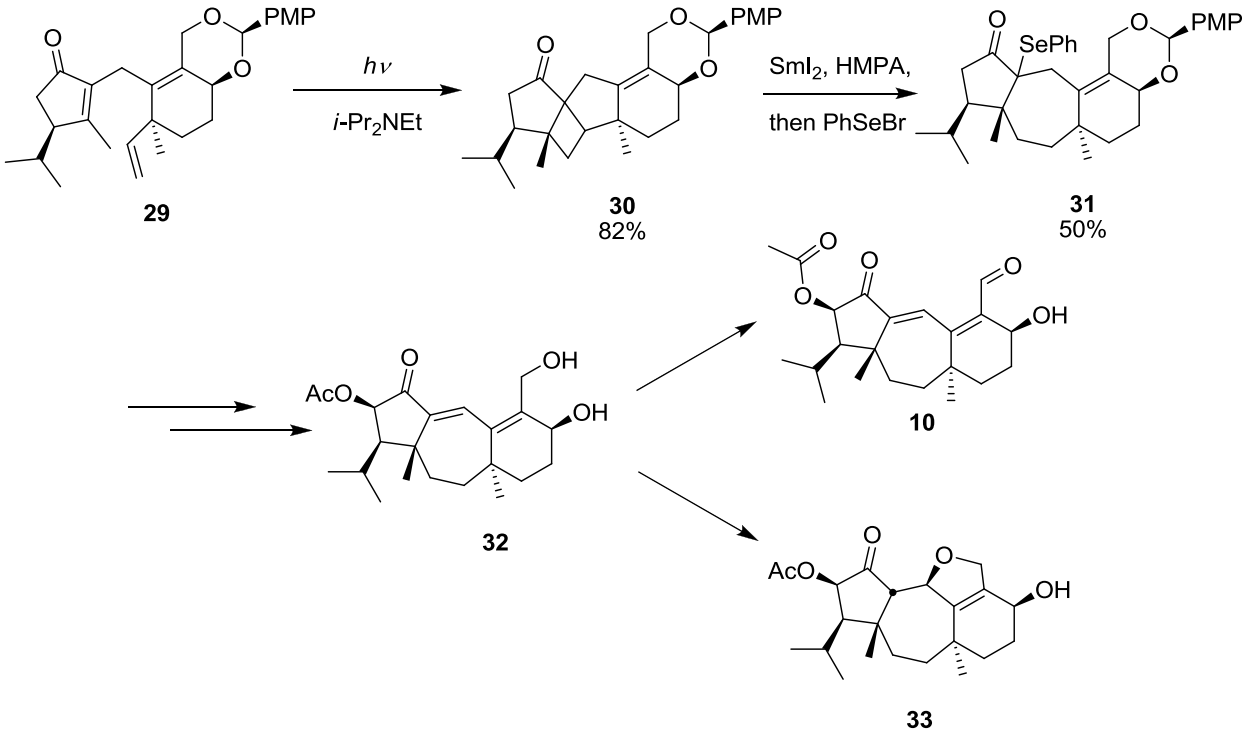
In 2005, Yang and coworkers[15] successfully synthesized the core of guanacastepene A **10** through the use of an intramolecular Diels-Alder reaction. The reaction consisted of an alkyne acting as dienophile across a tethered furan ring to provide tetracycle **27** in good yields. The cycloether was then cleaved using trimethyl

aluminum, which provided a regioselective methylation and ring opening to yield the tricyclic core **28**. This exemplifies an interesting approach to the formation of the seven-membered ring, as it itself is not directly formed from the Diels-Alder reaction, but as a consequence of the placement of the reacting moieties.



26 **27** 80% **28** 62%

Scheme 5 – Yang's Approach to Guanacastepene A

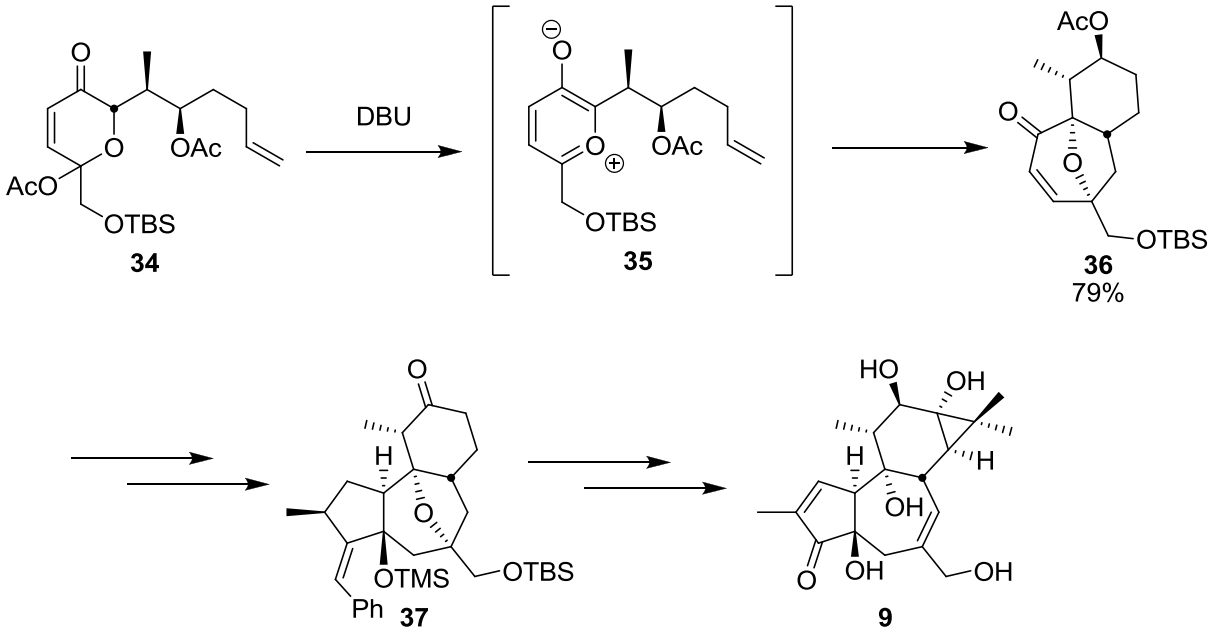


29 **30** 82% **31** 50% **10** **32** **33**

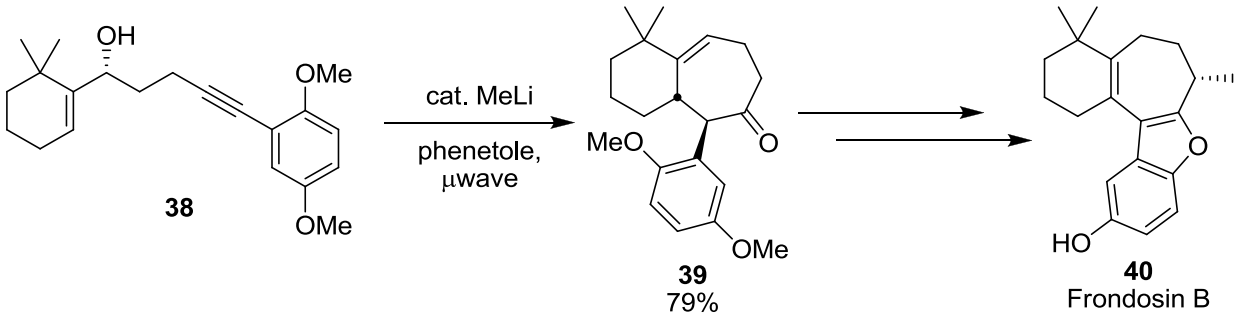
Scheme 6 – Sorensen's Synthesis of Guanacastepenes A and E

E. J. Sorensen completed a synthesis of both guanacastepenes A (**10**) and E (**33**) in 2006[16] employing a method similar to that of Winkler's synthesis of ingenol ten years prior. Upon synthesizing tricycle **29**, he subjected it to irradiation to promote a [2+2] photocycloaddition between the olefin of the five-membered ring and the pendant alkene of the cyclohexene moiety. This provided cyclobutane **30** as a single stereoisomer at the methyl group, presumably controlled by the steric hindrance of the top face by the isopropyl group. Following the successful photocycloaddition, samarium iodide-mediated fragmentation proved successful with the resulting samarium enolate being trapped with phenylselenenyl bromide. A series of transformations provided diol **32**, which could be transformed either to guanacastepene A **10** according to Danishefsky's previous studies,[17] or guanacastepene E **33**. This marked the first successful synthesis of (-)-guanacastepene E.

Wender used a new approach to the formation of seven-membered carbocycles by cycloaddition.[18] In the first asymmetric synthesis of phorbol **9**, he utilized a cycloaddition across oxidopyrylium ion **35** to accomplish a [3+2] cycloaddition. Tricycle **36** was formed as a single diastereomer; the transition state likely involves the tether between the oxidopyrylium moiety and the alkene adopting a chair conformation, placing the methyl group in an equatorial position to minimize steric effects with the carbonyl.[18] This transformation provides two new useful carbocycles that will go on to form the core of phorbol, and the ether cyclic ether, upon cleavage, provides the necessary alcohol in the correct orientation. The racemate of cyclic ether **37** was previously transformed to racemic phorbol **9,**[19] and the synthesis was improved upon in addition to creating an asymmetric product.



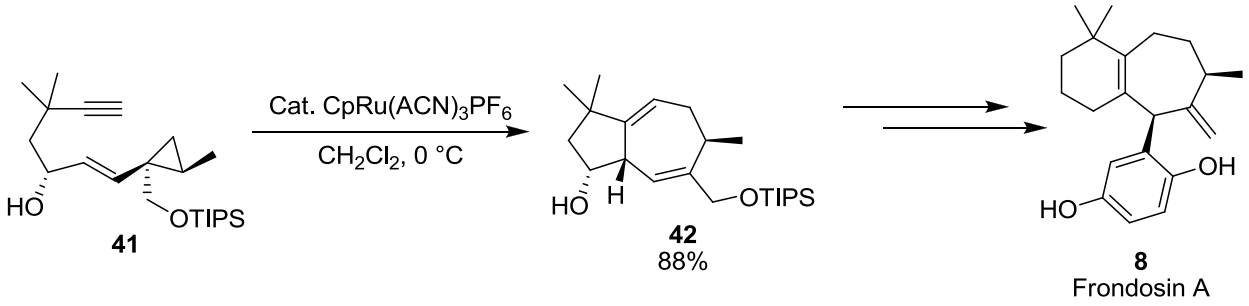
Scheme 7 – Wender's Formal Synthesis of Phorbol



Scheme 8 – Ovaska's Total Synthesis of (-)-Frondosin B

Ovaska completed the total synthesis of (-)-frondosin B via a sequential oxyanionic 5-exo-dig cyclization and Claisen rearrangement in 2009 during his studies on

the asymmetric synthesis of seven-membered carbocyclic rings.[20] The synthesis resulted in a slight improvement over the previous syntheses of Danishefsky[21] and Trauner,[22] and provided a new methodology for the synthesis of seven-membered carbocycles in an asymmetric fashion. The method appears to be general for relatively simple compounds similar to **38**, which were synthesized via Corey-Bakshi-Shibata reduction.[23] Of particular interest to this approach is that two new chiral centres are created in one reaction under complete stereocontrol, and the method is excellent for the formation of a 6,7-bicyclic system. The syntheses of such starting materials are not trivial, however, and only five- and six-membered cyclic allylic alcohols were tested using this methodology. Methyl lithium is also quite reactive, and the use of a catalytic amount may cause unwanted side-reactions if not accounted for.



Scheme 9 – Trost's Total Synthesis of (+)-Frondosin A

Following the discovery of the rhodium-catalyzed [5+2] cycloaddition reaction by Wender,[24] Trost developed the ruthenium-catalyzed variant and has studied it in detail for the last decade,[25] applying the methodology towards the total synthesis of (+)-frondosin

A **8**.[26] The work of Wender and Trost will be discussed in detail in upcoming sections, however the total synthesis perfectly illustrates the utility of this type of reaction in organic synthesis in general. The key step involves the cycloaddition between a vinylcyclopropane and alkyne under the catalysis of a half-sandwich ruthenium complex, and proceeds regioselectively and with high yields. Following this step, a ring-expansion using $TMSCHN_2$ was accomplished to provide the (5,6)-bicyclic core of **8**. This synthesis is reported as the first total synthesis of frondosin A.

2.1.1 – The Perezone-Pipitzol Rearrangement

Likely the first example of a [5+2]-type rearrangement occurred in 1885[27] completely unknowingly, and remained a mystery until almost a century after its initial discovery. Dubbed the Perezone-Pipitzol rearrangement, it was the thermal transformation of perezone **43** into pipitzol **45/46**. Anschutz and Leather reacted the silver salt of perezone, whose structure was unknown at the time, with ethylene bromide to provide the rearrangement below as a 1:1 mixture of **45** and **46**. It was not until almost 100 years later that Joseph-Nathan determined the structure of the products of this reaction, although it had been confirmed that the reaction could proceed directly from perezone **43** by heating in excess of 200 °C,[28] and that the product was an isomer of the starting material.[29] Joseph-Nathan initially proposed mechanisms based on an incorrect characterization of perezone, although later that year the correct structure was elucidated, allowing for his correct deduction that the reaction proceeded through a concerted mechanism, formally a [5+2] cycloaddition.

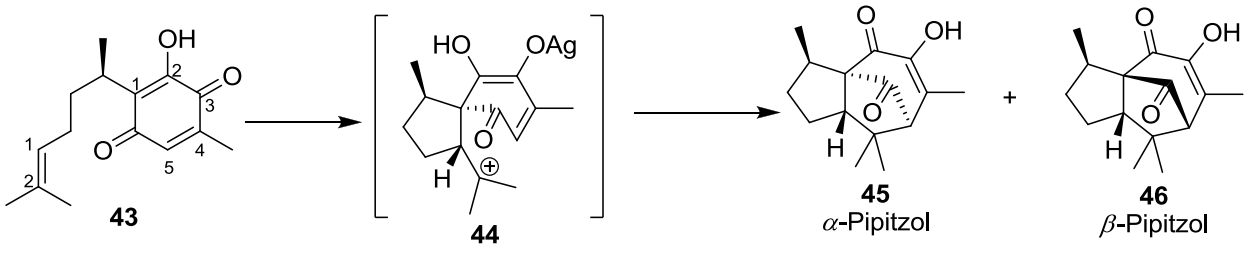
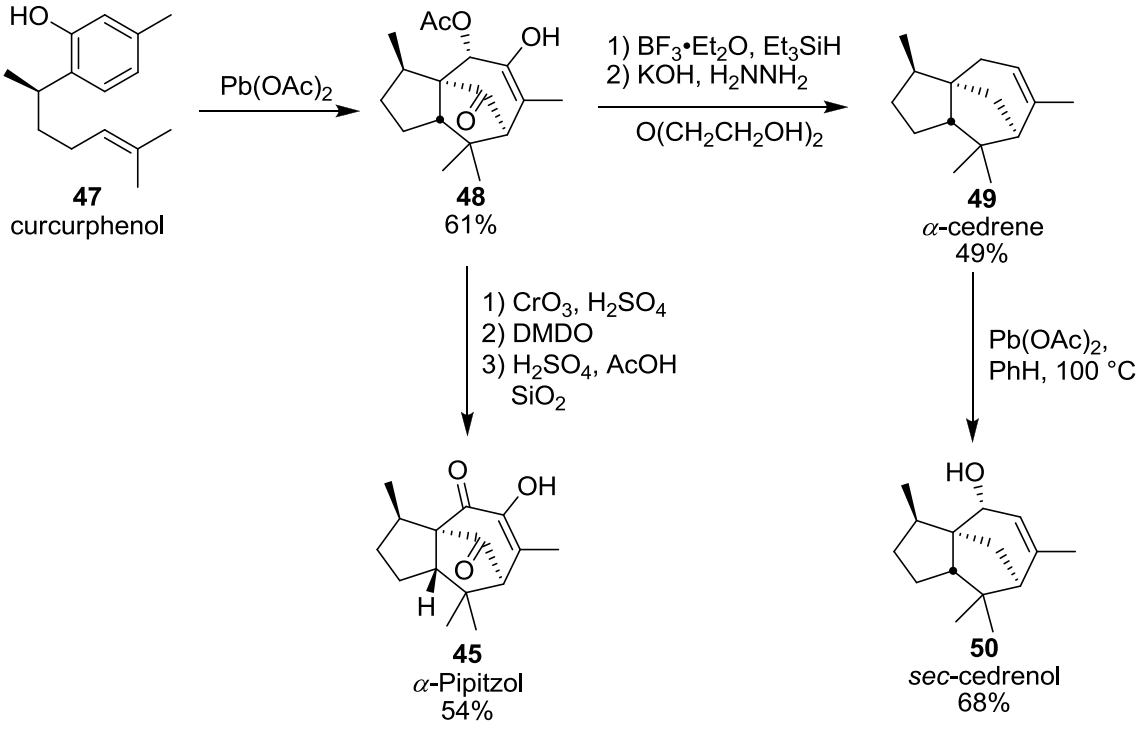


Figure 2 – The Perezone-Pipitzol Rearrangement

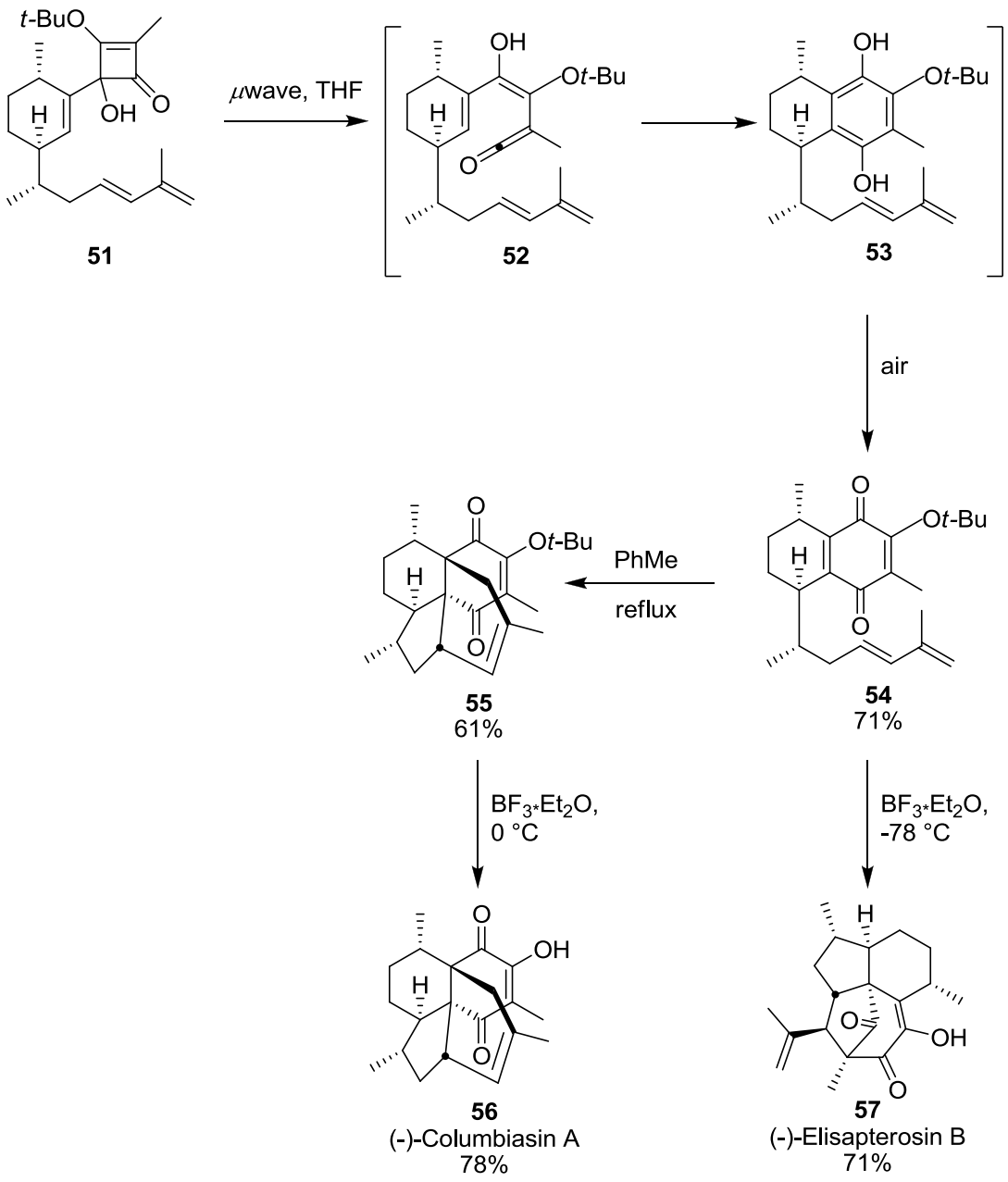
Currently, there are a number of examples of this type of reaction in the literature. These reactions are typically conducted under Lewis-acidic conditions, such as BF_3•OEt_2,

which favours the formation of α-pipitzol in the traditional reaction.[30] This selectivity has been proven to arise from a shift towards a stepwise mechanism, which can be mediated by using a different Lewis acid such as $AlCl_3 \bullet SEt_2$.[31]

In natural product synthesis, this reaction has limited use, as it requires specific substrates to function well. The most common version of this reaction when done intramolecularly is through the oxidation of phenolic substrates to produce an *ortho*-quinone, which can undergo the rearrangement. An elegant example comes from Pettus,[32] who used this rearrangement to synthesize α-pipitzol **45**, α-cedrene **49** and *sec*-cedrenol **50** in one sequence, as illustrated in **Scheme 10**.



Scheme 10 – Pettus' Biomimetic Synthesis of *sec*-Cedrenol



Scheme 11 – Harrowven's Synthesis of (-)-Columbiasin A and (-)-Elisapterosin B

Another notable example of this transformation includes Harrowven's total syntheses of (-)-columbiasin A and (-)-elisapterosin B,[33] one of which has the perezone-type [5+2] cycloaddition as a late-stage transformation in good yields and diastereoselectivity. The syntheses began with (-)-carvone and proceeded with 12 and 11

steps, respectively. Of particular interest is the fact that quinone **54** could undergo two different cycloaddition reactions; one [5+2] under Lewis acidic conditions, which removed the *tert*-butyl group from the hydroxyl moiety as well as initiated a cycloaddition, and one Diels-Alder under thermal conditions, which necessitated removal of the *tert*-butyl group under the same conditions as the [5+2] reaction.

2.2 – The [5+2] Cycloaddition Reaction

As shown in the previous section, the [5+2] cycloaddition is, in general, the reaction between a five-membered dipolarophile moiety and a unit of unsaturation. Both inter- and intramolecular processes have been developed,[3] however the intramolecular reaction has received much more attention in the synthetic community, as it allows the regio- and often stereospecific formation of bicyclic systems in one step.[11] The formal mechanism of the reaction is presented in **Figure 3**, with a vinylcyclopropane acting as the five-membered component. The metal-catalysed reaction has a slightly different mechanism, proposed by Wender.[34]

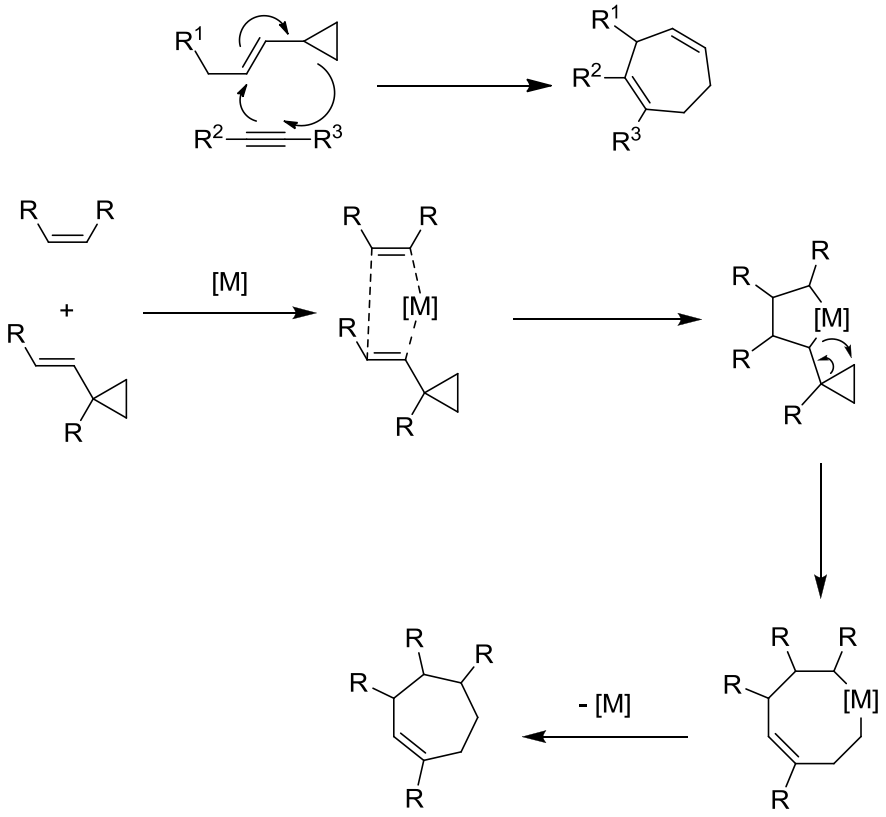
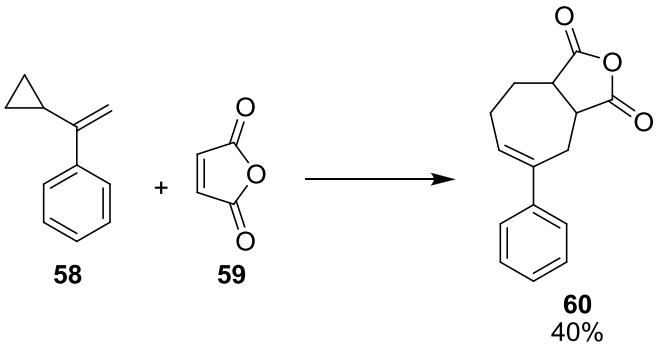


Figure 3 – Mechanism of the [5+2] Cycloaddition

As with any cycloaddition reaction, the cyclic array of electrons allows for the bonds to be formed and broken near-simultaneously, which avoids the problems associated with entropy and non-bonding intermediate transition states for cyclizations to form seven-membered rings that are not pericyclic reactions.[12] In the metal-catalyzed reaction, the transition metal oxidatively inserts itself between the two olefin moieties and ring strain causes the collapse of the cyclopropane ring. The metal is then reductively eliminated, joining the two fragments of the molecule together to form a seven-membered ring.

The first intentional example of a [5+2] cycloaddition was reported by Sarel in 1959,[35] where he reacted α-cyclopropyl styrene **58** with maleic anhydride **59** in dry benzene to afford cycloadduct **60**. He goes on to state that there is a large quantity of evidence supporting the "conjugated-like" character of these cyclopropyl groups with nearby olefins, in that they act analogous to unsaturated carbon-carbon bonds. When sufficiently activated, such as with a phenyl group, they can undergo a reaction mechanistically similar to the Diels-Alder cycloaddition. Of particular interest is that there was no catalyst required, and 17% of an insoluble *bis*-adduct was recovered from the reaction mixture which contained no phenyl rings. Unfortunately this reaction proved to be irreproducible in the hands of others,[36] and research in this area was scarce until the discovery of the previously-discussed Perezone-Pipitzol rearrangement.



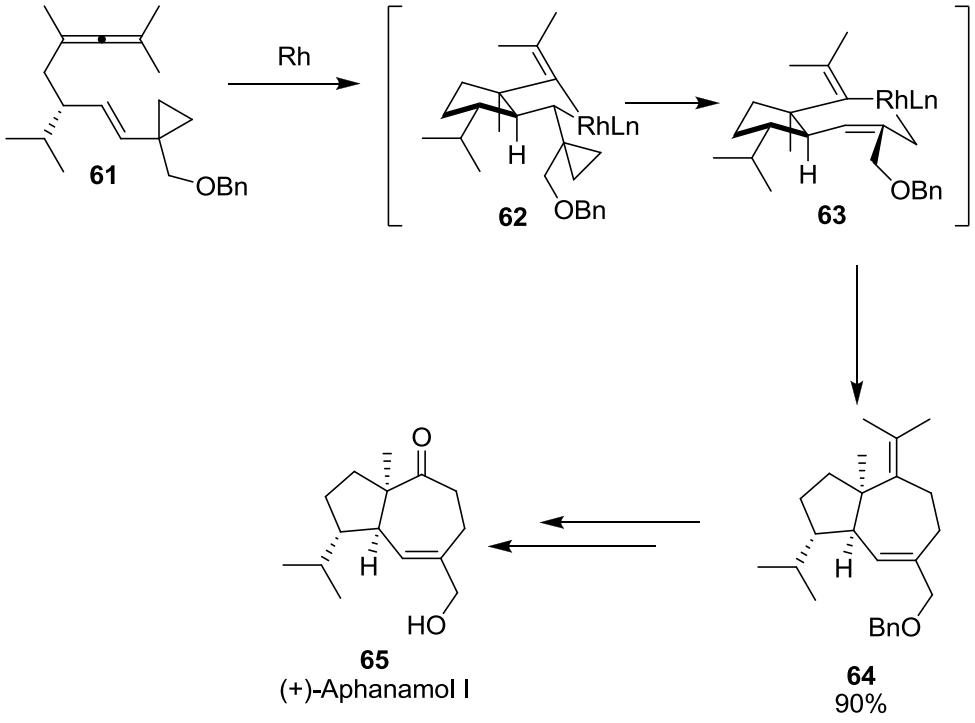
Scheme 12 – Sarel's Initial [5+2] Cycloaddition

2.2.1 – Intramolecular [5+2]-Cycloaddition Reactions

Intramolecular cycloadditions of this type have seen wide usage in natural product synthesis, as they allow for the expedient formation of bi- or tricyclic carbocycles and represent a tremendous increase in complexity in a single step. The tethering of both reactive species provides greater reactivity, and reactions that fail completely intermolecularly may succeed when done intramolecularly.[3] The first reported intramolecular transition metal-catalyzed [5+2] cycloaddition was performed by Wender in 1995[24] and represents the basis from which this chemistry was developed in the following years. While the Perezone-Pipitzol rearrangement can be considered the first formal [5+2] reaction and Sarel was likely the first to accomplish the cycloaddition between a vinylcyclopropyl moiety and an unsaturated carbon unit, the detailed study on the scope and mechanism by Wender is generally considered to be the beginning of the [5+2] cycloaddition.[37] In the following sections, the important reactions of this type will be examined, notably Wender's Rh-based intramolecular cycloaddition and Trost's follow-up work with Ru-based catalysts.[38-39]

2.2.1.1 – Wender's Rh-Catalyzed [5+2] Cycloadditions of Vinylcyclopropanes

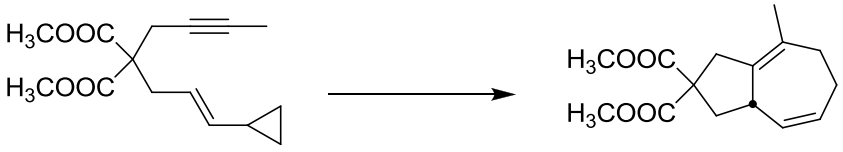
As discussed briefly in the introduction to this section, Wender was the first researcher to discover the transition metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes and carbon-carbon unsaturation.[24] He went on to become a pioneer in this field, studying many different substrates and several catalyst systems. He has proposed several mechanisms for this transformation, one of which is illustrated in **Scheme 13** below in his total synthesis of (+)-apahanamol I.[34] This work served as the inspiration for Hudlicky's attempts at the [5+2] reaction,[3] and led to the current project.



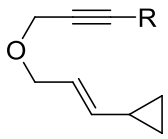
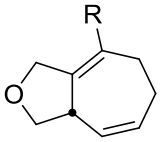
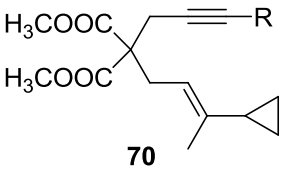
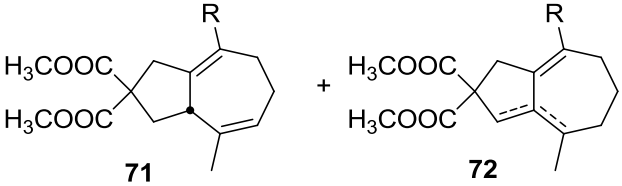
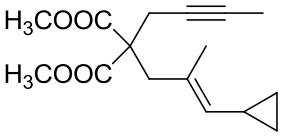
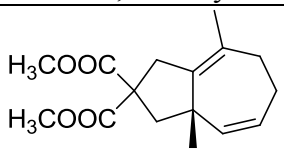
Scheme 13 – Wender's Synthesis of (+)-Aphanamol I

In his initial studies on the intramolecular [5+2] catalyzed by rhodium,[24] Wender discovered that substrates tethered with an ether linkage or a carbon bearing electron-withdrawing groups were suitable substrates, and this methodology could create (5,7)-fused ring systems in high yields with good selectivities. The rhodium catalyst would undergo a change in his future endeavors, with most of his later research on the topic focussing on rhodium (I) dimers such as $[Rh(CO)_2Cl]_2$ (**3**).[37] Wender also discovered the first intermolecular [5+2] reaction of simple vinylcyclopropanes using transition metal catalysis, and the substrate scope was found to be quite tolerant on the alkyne side.[37] Wender determined that an alcohol protected with TBDMS appended to the vinylcyclopropane could be used as a synthetic handle for further transformations and found that the reaction was tolerant of ketones, ethers, esters, silanes and other cyclopropanes attached to the alkyne (**Scheme 14**). The intermolecular process did not proceed at all with the previously-used Wilkinson's catalyst. A mechanistic diagram is presented in **Figure 4**.

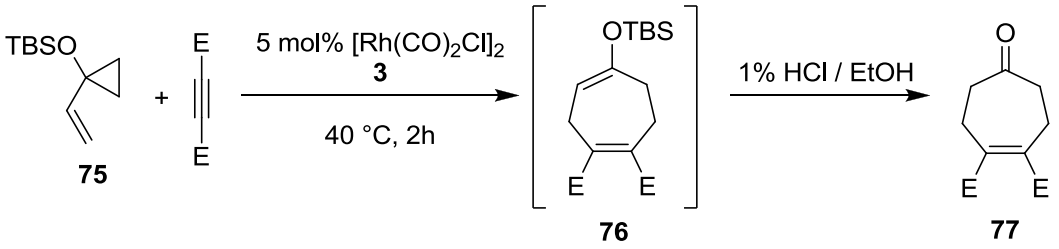
Table 1 – Wender's Initial [5+2] Study



66 **67**

Entry	Vinylcyclopropane	Cycloadduct	Conditions
1	**66**	**67**, 83%	A, 20 min
2	**66**	**67**, 84%	B, 2d
	 **68**	 **69**	
3	R=Me	88%	B, 1.5h
4	R=TMS	83%	B, 3.5h
5	R=CO_2Me	74%	B, 1.25h
6	R=Ph	80%	B, 1.5h
7	R=H	50%	C, 1.5h
	 **70**	 **71** **72**	
8	R=Me	89%, 3.5:1	B, 2d
9	R=Me	92%, 1:2	D, 2.5h
10	R=H	82%, **74** only	B, 2d
11	R=CO_2Me	81%, **74** only	B, 16h
12	R=TMS	71%, **75** only	B, 7d
	 **73**	 **74**	
13		82%	D, 0.5h

A = 0.5 mol% $RhCl(PPh_3)_3$, 0.5 mol% AgOTf, PhMe, 110 °C.
B = 10 mol% $RhCl(PPh_3)_3$, PhMe, 110 °C.
C = 10 mol% $RhCl(PPh_3)_3$, THF, 100 °C.
D = 10 mol% $RhCl(PPh_3)_3$, 10 mol% AgOTf, PhMe, 110 °C.



Scheme 14 – Wender's Intermolecular [5+2] Cycloaddition

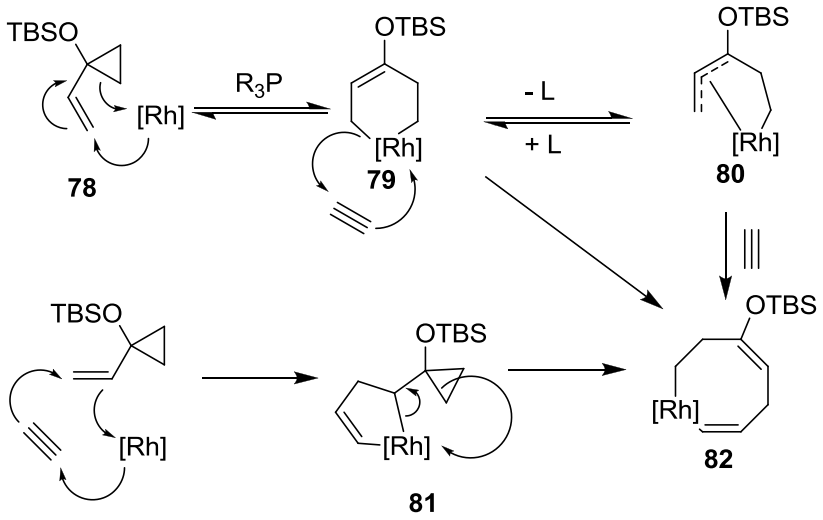
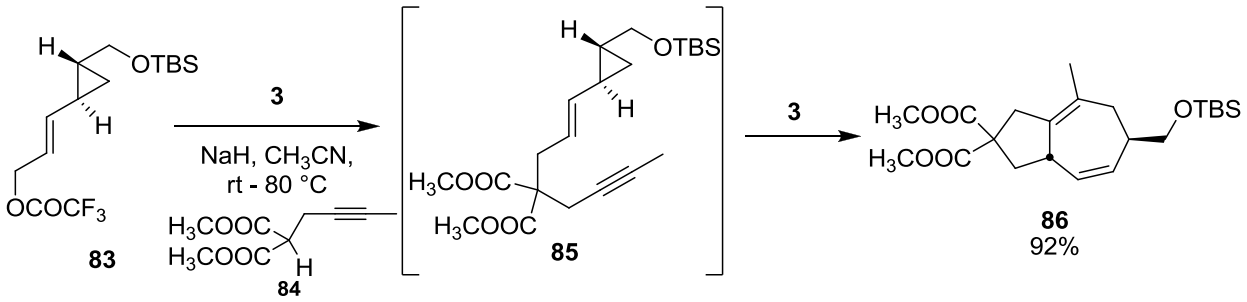


Figure 4 – Wender's Proposed Mechanisms for [5+2]

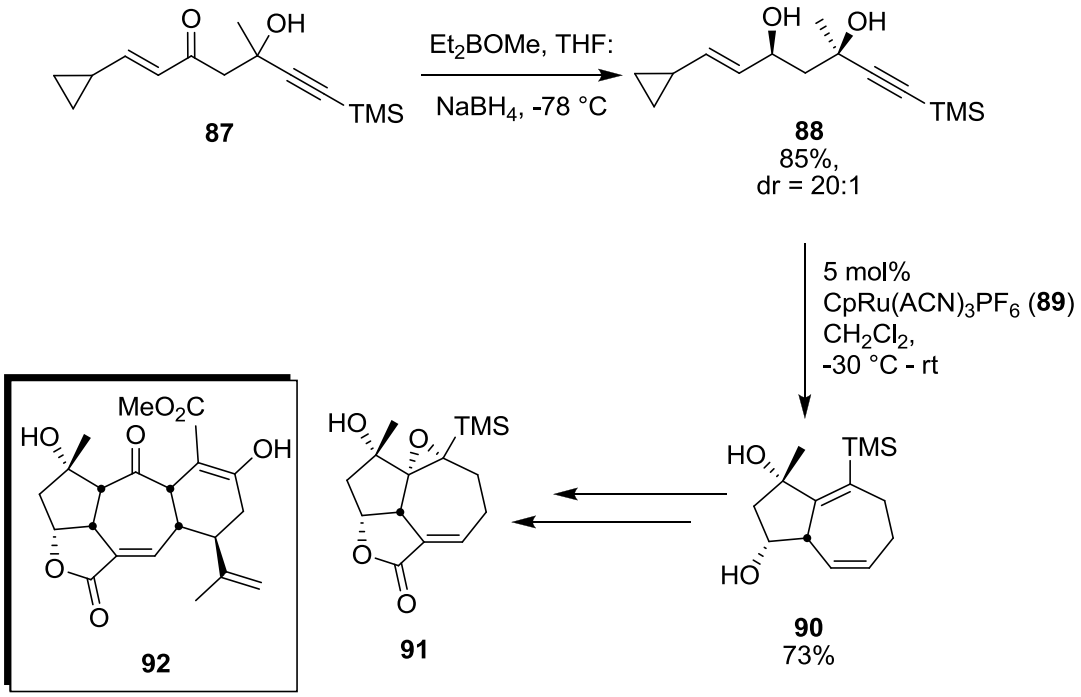
Martin and coworkers have added to this reaction manifold, developing a sequential asymmetric allylation – [5+2] cycloaddition methodology (**Scheme 15**).[40] The reaction proceeds in excellent yields and selectivity, providing mostly a single regioisomer and asymmetric products when using asymmetric substrates. The scope of the allylation appears to be quite good, although no sequential reactions were attempted that were not malonate esters similar to vinylcyclopropane **85**.



Scheme 15 – Martin's Sequential Allylation – Cycloaddition Methodology

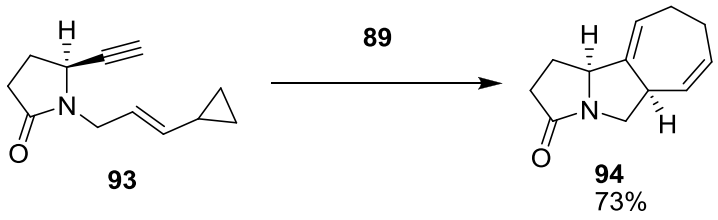
2.2.1.2 – Trost's Ru-Catalyzed [5+2] Cycloadditions

Trost is another prominent contributor to the field of vinylcyclopropane [5+2] cycloadditions. As in the studies performed by Wender, Trost examined several other metals as catalysts and has been doing many studies with the ruthenium-catalyzed reaction.[25] Aside from methodology work, Trost has also used this type of cycloaddition reaction in several synthetic plans. Aside from the aforementioned total synthesis of (+)-frondosin A (**Scheme 9**),[26] Trost has also begun an approach towards the synthesis of rameswaralide **92**,[38] the key step of which is a [5+2] cycloaddition as shown in **Scheme 16**.



Scheme 16 – Trost's Approaches to the Synthesis of Rameswaralide

Trost's variant on the rhodium-catalyzed [5+2] shares many similarities in substrate scope, but has never been demonstrated on an intermolecular reaction. It is thought that the ruthenium-catalyzed reaction proceeds via a five-membered metallacycle of the type **81** (**Figure 4**), in contrast to what is currently accepted for the rhodium variant. This is evidenced by E- and Z-olefins reacting at different rates with ruthenium, while no differences in reactivity are observed when using rhodium catalysts.[39]



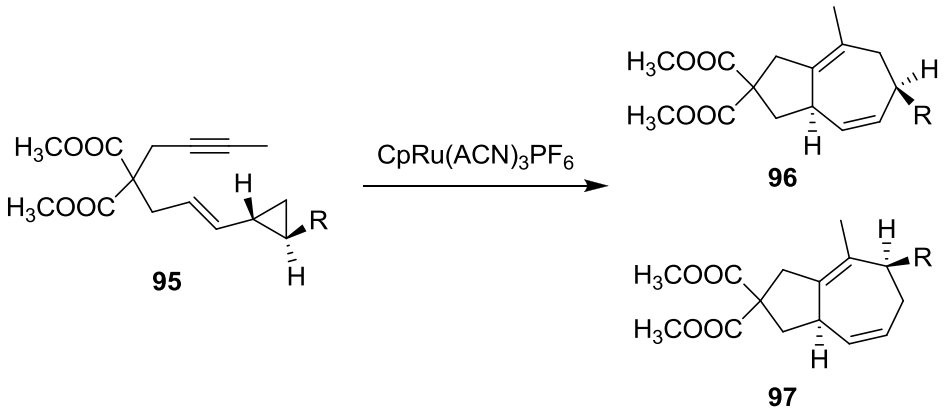
Scheme 17 – [5+2] Cycloaddition of Amide 93

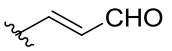
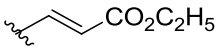
One particularly attractive benefit of the ruthenium-catalyzed [5+2] is that it has been shown to react with amides and tosylamides and lactams.[39] This opens the possibility of synthesizing additional natural products, such as alkaloids, and although the scope is thus far untested it does suggest that there are many uses for this type of catalyst system that have not yet been discovered.

The regioselectivity of this reaction can be difficult to predict, and appears to change radically from one substrate to the next. Trost performed a study comparing several catalysts and substrates and discovered that the metal centre itself is not as important as the size and electronic structure of the ligands surrounding it, explaining the difference between his catalyst system and those used by Wender.[25] The addition of an indium co-catalyst can occasionally increase regioselectivity, as shown in **Table 2**,

however the effects of this are unexplained and do not appear to follow a distinct pattern. In general, there appears to be a very slight preference for the more substituted bond of the cyclopropane migrating; entries 1 and 2 are somewhat anomalous, as they show excellent selectivity when an aldehyde is present on the cyclopropyl group. Small ethers and tosylates provide very little regioselectivity. Silyl ethers have the potential to preferentially provide the more substituted carbon migration, however it appears that the larger silyl groups are required.

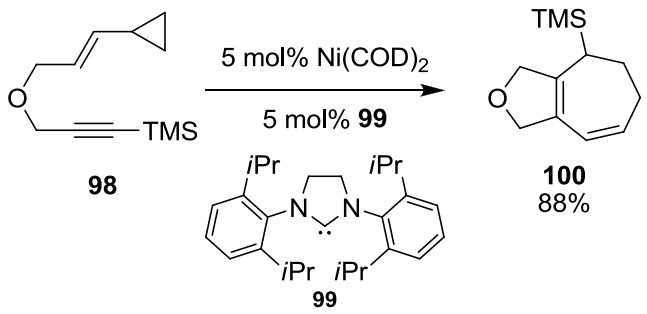
Table 2 – Regioselectivity of Ruthenium-Catalyzed [5+2] Cycloaddition



Entry	R	Additive	Time	Ratio 96:97	Isolated Yield
1	CHO	None	0.5h	1:12	83%
2	CHO	10 mol% $In(OSO_2CF_3)$	2h	1:15	83%
3	CO_2CH_3	None	2h	1:2	90%
4	CO_2CH_3	None	2h	1:2.5	88%
5	CO_2CH_3	10 mol% $In(OSO_2CF_3)$	2h	1:2.3	80%
6	$COCH_3$	None	3h	1.5:1	83%
7	$COCH_3$	10 mol% $In(OSO_2CF_3)$	3h	1:1.2	88%
8	CN	None	2h	1:1.9	87%
9	SO_2Ph	None	2h	1:1	78%
10		None	0.5h	1:1.6	82%
11		None	1h	1:1.6	87%
12	C=CH	None	2h	1:2.5	85%
13	$CH_2OTBDMS$	None	2h	1:1	90%
14	CH_2OTIPS	None	2h	3:1	81%
15	CH_2OTIPS	None	2h	2:1	88%

2.3 – Miscellaneous [5+2]-Cycloaddition Reactions

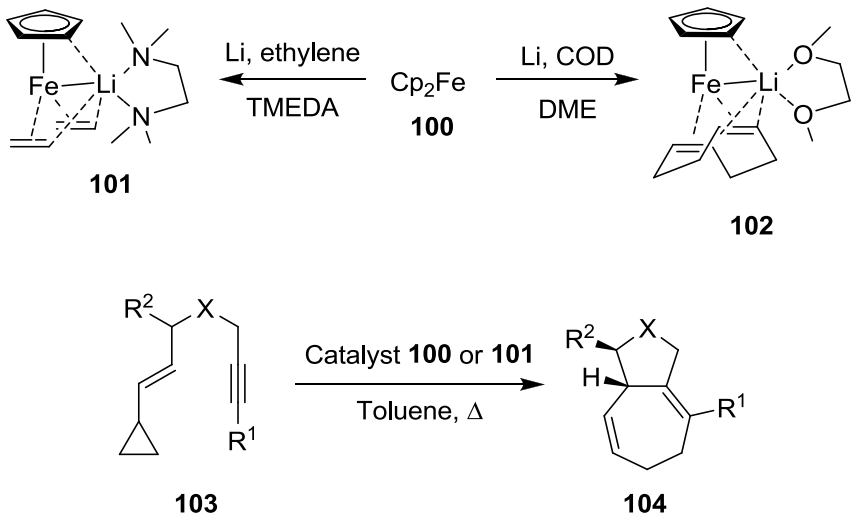
Zuo and coworkers have developed a nickel-mediated vinylcyclopropane [5+2] cycloaddition, wherein a Ni-NHC complex is formed *in situ*.[41] The chemistry has not yet been explored in great detail, but could possibly become a cheaper alternative to expensive rhodium or ruthenium catalysts.



Scheme 18 – Zuo's Ni-NHC-Catalyzed [5+2] Cycloaddition

Similarly, Furstner has been developing iron catalysts for the use in such reactions, but it has not been explored in great detail as of yet, having only been attempted with malonate esters (**Scheme 19**, X = $(C(CO_2Me)_2)$.[42] Additionally, the iron complexes formed do not appear to be very selective. They are known to undergo a wide array of cycloadditions, cycloisomerizations and other related reactions, including coupling between olefins and alkynes. This promiscuity could lead to unwanted side-reactions. The metal complex must also be synthesized prior to undergoing to the reaction, as it is not commercially available. Although complex **101** was synthesized on 85g scale, the yield was 50% after recrystallization. Catalysts **100** and **101** were both successful in promoting the desired cycloaddition on several example substrates, but the range was somewhat

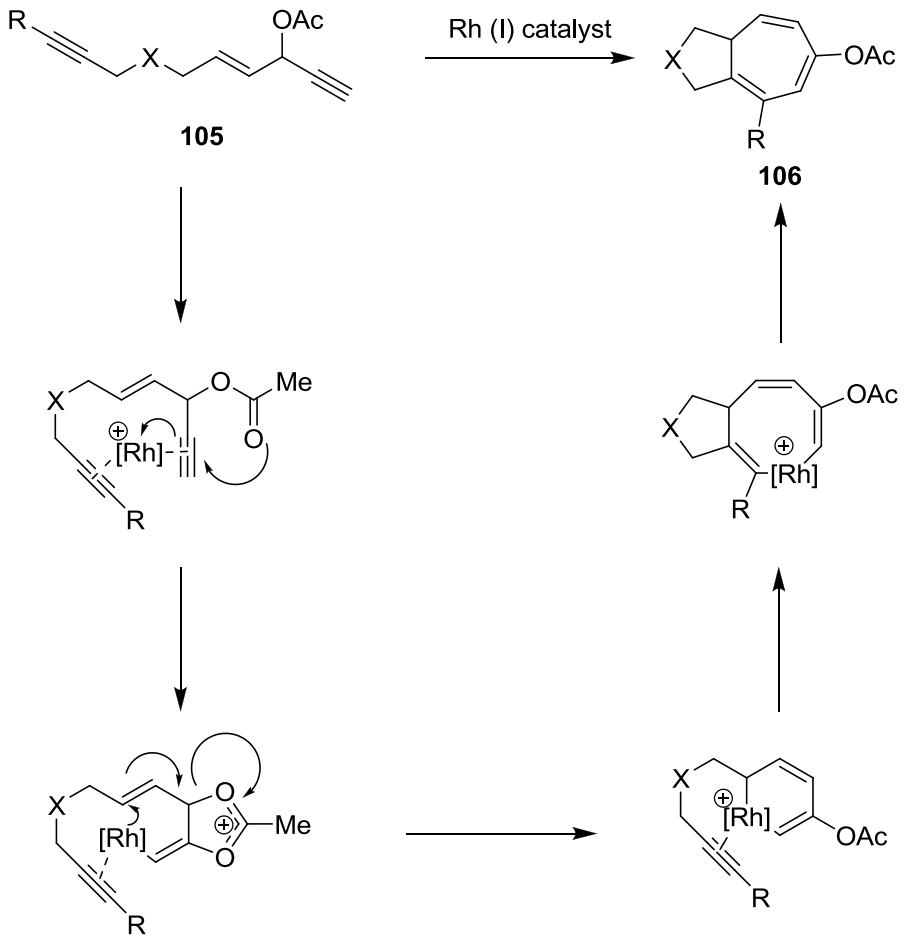
limited (R_1 = H, TMS, Aryl, R_2 = H, Me). The reaction did show preference for the *cis*-orientation as shown in compound **103** when R^2 was a methyl group.



Scheme 19 – Iron Complexes for [5+2] Reactions

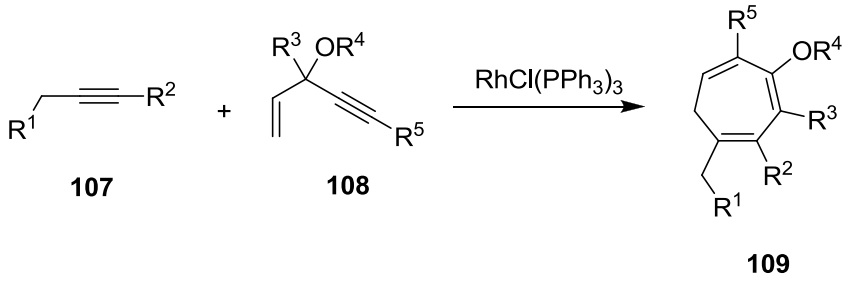
Tang and coworkers recently developed[43] a new type of [5+2] cycloaddition reaction involving a tethered acyloxy ene-diyne system with subsequent migration of the acyloxy group to provide seven-membered rings as shown in **Scheme 20**. The initial scope was limited to intramolecular reactions where one of the alkynes was necessarily terminal; however, recently the scope was expanded to include an intermolecular variant and substituted alkynes.[44] The tether itself was well-explored, and the reaction tolerated ethers, tosylamides, diesters and methylene linkers. The reaction proceeded well with several rhodium (I) catalysts, most notably $[Rh(CO)_2Cl]_2$ and $[Rh(COD)_2]BF_4$.

The reaction was also successful when performed intermolecularly (**Scheme 21**), with a wide variety of alkynes being explored, both terminal and internal. Yields ranged from 65-90%,



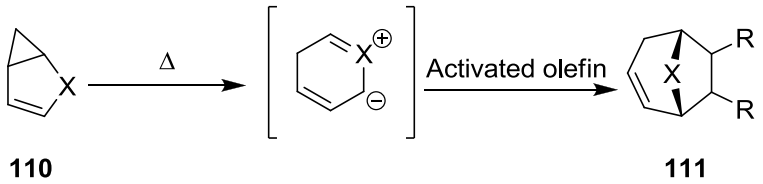
Scheme 20 – Tang's [5+2]-Acyloxy Migration

and many functionalities on the alkynyl moiety were tolerated, from alcohols and tosylamides to halides and esters. Interestingly, the most successful catalyst for the intermolecular reaction proved to be Wilkinson's catalyst ($RhCl(PPh_3)_3$).



Scheme 21 – Tang's Intermolecular [5+2] Cycloaddition

An interesting, albeit underexplored, [5+2]-cycloaddition reaction is the intermolecular reaction of a fused bicyclic system with activated electrophiles.[45] This serves as the only example of this type of reaction where the vinylcyclopropane is constrained to a ring aside from the recent example by Hudlicky.[3] The reaction was not well-explored, and only extremely activated olefins were successfully transformed, such as tetracyanoethylene or DMAD. Of particular interest is the lack of catalyst and that only heterocycles were successful (X = O, N, S).



Scheme 22 – Strained Bicyclic Intermolecular [5+2] Cycloadditions

3. Results and Discussion

3.1 – Introduction

As outlined in the introduction, Hudlicky had previously shown that vinylcyclopropanes of the type **6** (**Scheme 1**) could successfully undergo the intramolecular [5+2] cycloaddition reaction in very low yields after extremely long reaction times.[3] It was thought that the stability of the substrates was due to the olefin of the vinylcyclopropane being constrained to a ring, which does not support a planar vinylcyclopropane moiety as the cyclopropane is less sterically congested in an orientation orthogonal to the alkene.[3] In order to test that hypothesis, a simple model system was devised containing a vinylcyclopropane with the olefin moiety constrained in a cyclohexene ring, with variable substitution on the tethered alkyne in an attempt to determine substrate tolerance. The substrates to be tested are shown in **Figure 5**.

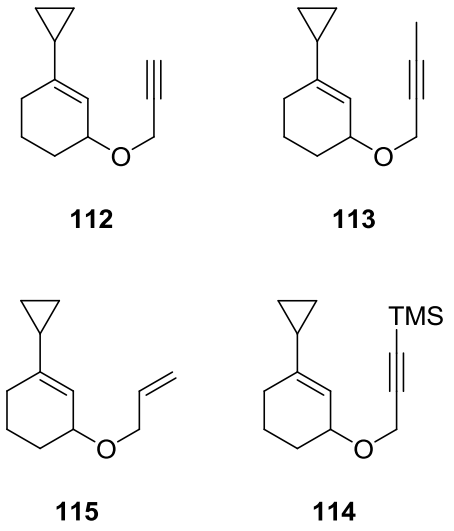
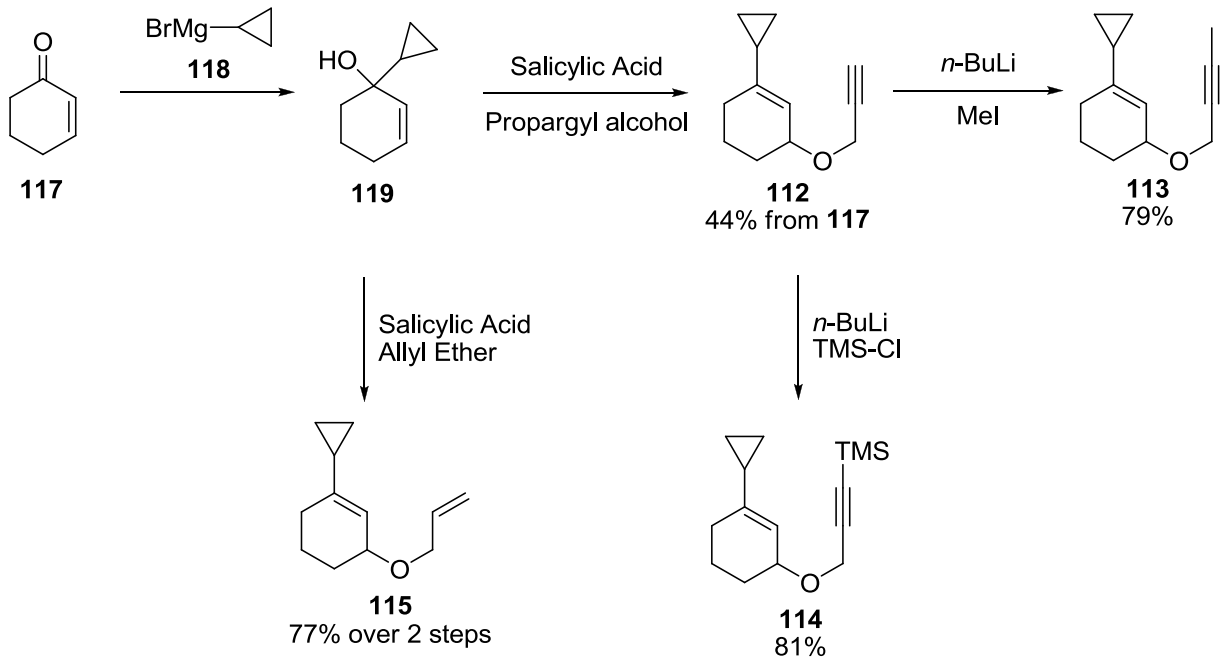


Figure 5 – Model Substrates for the [5+2] Cycloaddition

3.2 – Synthesis of 1-Cyclopropyl-Cyclohexenyl Substrates

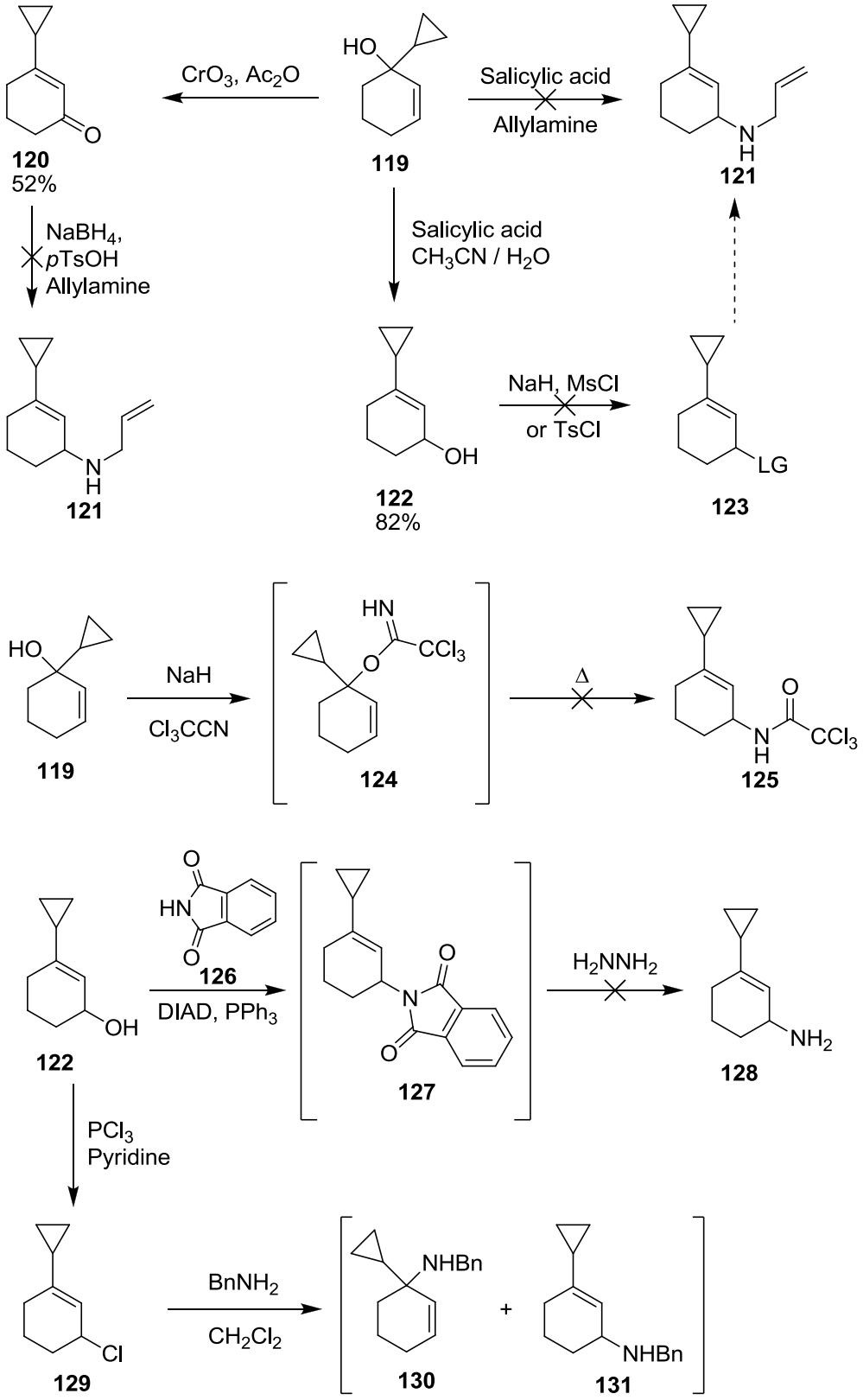
The substrates were synthesized according to **Scheme 23**. Cyclohexanone **117** underwent a standard Grignard reaction with cyclopropyl magnesium bromide **118** to provide vinyl alcohol **119**. Acid-catalyzed allylic transposition of the tertiary alcohol proceeded in moderate yields to provide the desired ether substrates **112**, **115** and **116** as shown. Terminal alkyne **112** was substituted with either methyl or trimethylsilane to finish the synthesis of the ethereal substrates.



Scheme 23 – Synthesis of Ether Substrates

In addition to ether substrates, amine and ester substrates were also initially planned for examining the substrate scope of the cycloaddition. Attempts at synthesizing

these substrates proved unsuccessful for various reasons, and the attempts are outlined in **Scheme 24** and **Figure 6**.



Scheme 24 – Attempts towards Amine Substrates

For the approaches to amine substrates, tertiary alcohol **119** underwent a Dauben-Michno oxidative transposition[47] to provide ketone **120** in moderate yield. Attempts at reductive amination provided primarily the 1,4-reduced product and significant decomposition of the starting material. Allylic transposition with water provided alcohol **122** in high yield, and it was thought that by transforming the alcohol into a leaving group, substitution with an amine reagent would be possible. Unfortunately, mesylation provided a mixture of volatile components which proved difficult to identify. Semi-crude NMR and MS data suggests a stripped-down mixture of compounds bereft of oxygen or chlorine, with several ^{1}H-NMR peaks between 3-5 ppm, and many broad peaks below 2 ppm. Direct allylic transposition failed using amine reagents, with the allylamine likely acting as a base rather than a nucleophile, inhibiting formation of the hydronium ion and stopping the alcohol from becoming a leaving group.

Attempted Overman rearrangement[48] also proved unsuccessful. The crude reaction mixture appeared to provide trichloroacetimide **124** in moderate yields and purity, however isolation attempts caused extensive decomposition, returning mostly starting material. Subjecting the crude material to rearrangement conditions led to an intractable mixture of products. The formation of phthalimide **127** was met with similar troubles, as the crude reaction mixture proved unstable to isolation and purification, and removal of the phthalimide moiety with hydrazine hydrate caused complete decomposition of the starting material with no identifiable products.

Attempted transformation of secondary alcohol **122** into an alkyl chloride was plagued with similar issues. The reaction proceeded in what appeared to be moderate purity; the upfield shift of the allylic proton and positive Beilstein test of the crude

mixture showed promising results, however isolation by column chromatography or distillation provided only trace amounts (>5%) of material not sufficiently pure for full characterization. The reaction provided the same profile by TLC and crude spectroscopy whether it was performed on the secondary alcohol **122** or tertiary alcohol **119**. Subsequent attempted substitution of the crude mixture using benzylamine proved similarly troublesome, but did provide what appeared to be a mixture of isomers **130** and **131** in roughly a 1 : 1 ratio based on crude NMR. These isomers also proved inseperable to chromatographic techniques, and distillation at ambient pressure or under vaccuum provided decomposition and loss of the volatile material, providing isolated yields of >10% of material not sufficiently pure for characterization. Spectroscopic analysis of the crude decomposition products suggested a total lack of alcohol, alkyl chloride, benzyl or amine substituents.

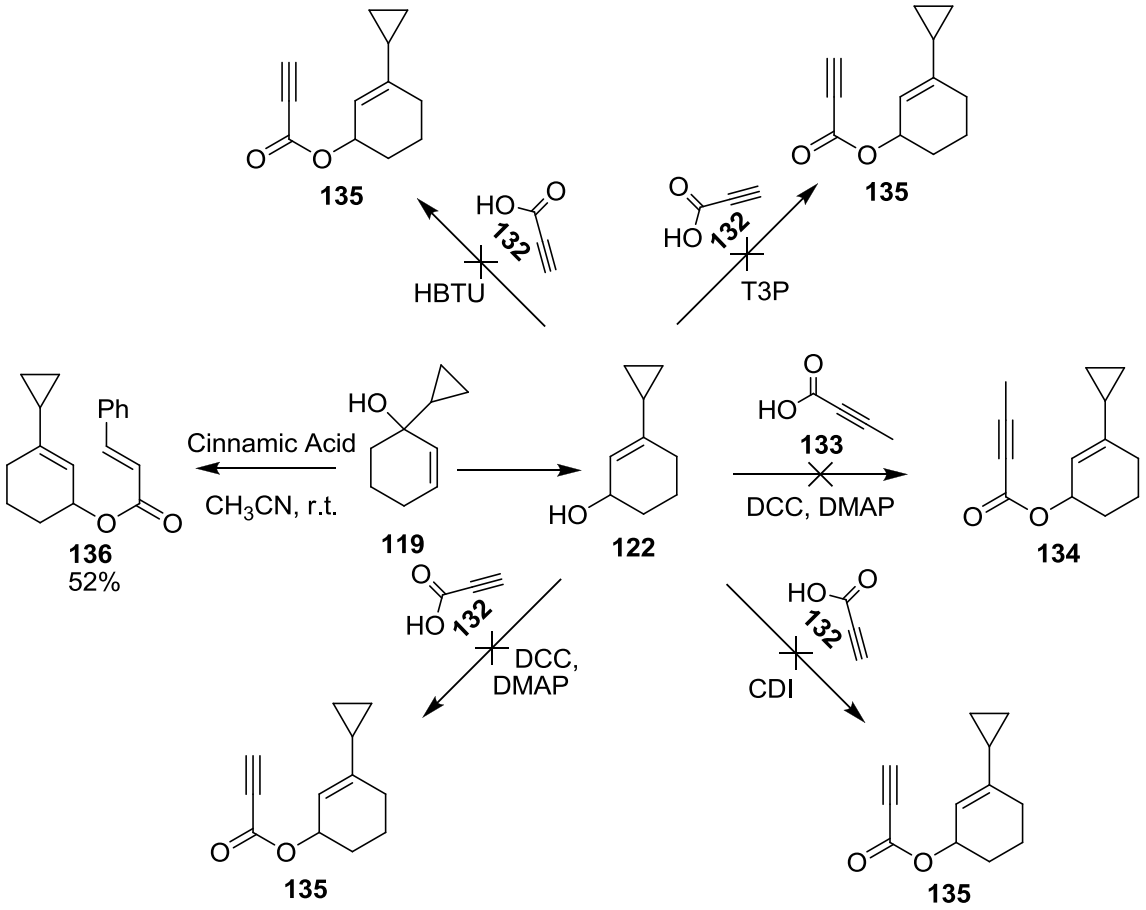


Figure 6 – Attempts towards Ester Substrates

Ester substrates were similarly troublesome. Allylic transposition of tertiary alcohol **119** using the acids themselves as both proton source and nucleophile proved somewhat successful with benzoic acid to form ester **136**, but not with either propiolic acid **132** or tetrolic acid **133**. A wide variety of coupling reagents were attempted, as pictured above, and although NMR analysis of the crude mixtures showed evidence that the esters were being formed for the DCC and HBTU reactions, a significant amount of starting material and unknown decomposition products emerged as well. Attempts to isolate the esters generally resulted in loss of the ester group, providing a mixture of the

initial alcohol and acid. Attempting to subject the crude mixture to a cycloaddition reaction provided no successful reactions, yielding only starting materials in very low yields as the sole isolable products.

3.3 – Cycloaddition Reactions of Allylic and Propargylic Ethers Derived from Various 1-Cyclopropyl-Cyclohexenyl Substrates

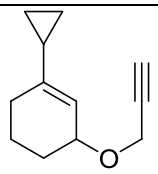
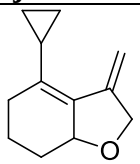
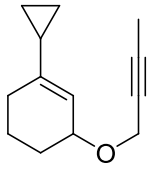
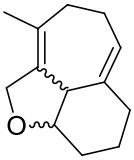
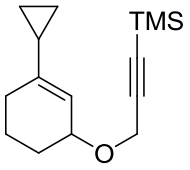
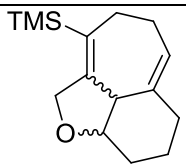
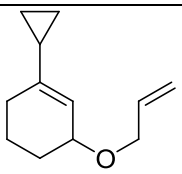
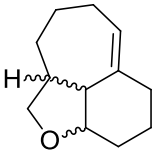
Several ether substrates were subjected to several catalysts for the [5+2] cycloaddition reaction, as well as several different conditions in attempts to promote other types of cycloadditions. Metal catalysts involving rhodium, ruthenium, palladium, zirconium, titanium, iron and copper were all attempted with varying degrees of success. The reaction of the Wender rhodium catalyst **3** with ether substrates is illustrated in **Table 3**. As can be seen from the table, the cycloaddition was not very successful for most substrates. Several did stand out, however, and only seemed to work with catalyst **3**. Notably, methyl propargyl ether **113** and allyl ether **115** underwent the cycloaddition with acceptable yields, although the products themselves proved difficult to handle in most cases due to volitility and instability. Cycloadduct **141** appeared to be the major product of the cycloaddition reaction, based on NMR and GC/MS studies; the GC showed four compounds all with a *m/z* = 178, which is expected, given that many new stereocentres give rise to stereoisomers in this reaction. Unfortunately, the product itself was quite volatile and unstable, frustrating attempts at isolation.

Ether **113** became the prototypical test substrate, as the product was the most stable during purification. The reaction did provide a mixture of *syn*- and *anti*-stereoisomers **139**, however. After several trials, the isomers could be separated and characterized using silica doped with silver nitrate.[49] Similar techniques with other substrates failed. A control reaction was run with unadorned vinylcyclopropane **122**, to

determine viability of the reaction. Providing low yields of 10-20%, likely due to volatility, the control reaction product had near-identical ^{1}H- and ^{13}C-NMR spectra, with the only notable difference a drastic downfield shift of *ca.* 1.5 ppm of the lone alkene proton. The exact mass of the isolated product was identical to that obtained from the starting alcohol. Whether this product arose from the isomerisation of the alkene or complexation of the olefin to the catalyst system is unclear.

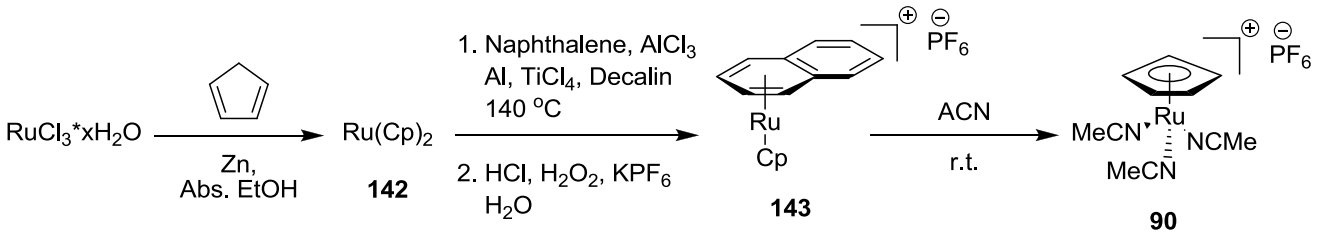
Alkynyl ether **112** provided compound **138** in low yield. This so-called "ene-yne coupling" product would become a constant byproduct of the [5+2] reactions with most substrates, often competing with the cycloaddition reaction itself. Low yields were attributed to this competition, and the resulting diene was rarely stable and often eluded characterization.

Table 3 – Ether Substrates in Rh-Catalyzed [5+2] Reactions

Substrate	Major Product	Yield
 **112**	 **138**	10-30%
 **113**	 **139**	35%
 **114**	 **140**	2%
 **115**	 **141**	46%

Reactions were carried out in a sealed tube in freshly-distilled 1,2-DCE at 88 ^{o}C with 10 mol% catalyst **3**.

Table 4 illustrates attempts at different reaction conditions for transformations involving methyl propargyl ether **113** and the terminal alkyne **112**. It's worth noting that Trost's catalyst **90**, the synthesis of which is shown in **Scheme 26**,[50] provided no conversion whatsoever.



Scheme 25 – Synthesis of Catalyst 90

Following Taber's work,[51] a [5+2+1] cycloaddition using iron (0) pentacarbonyl was attempted under an atmosphere of carbon monoxide and ultraviolet irradiation. Unfortunately this did not prove successful and the only recoverable product from the trials were unreacted starting material in low (~10%) yields. A blank reaction involving no iron catalyst under identical conditions provided a much higher recovery of starting material and minimal decomposition, and when attempted with no irradiation in the presence of the iron catalyst, a similar TLC profile compared to the catalyzed, irradiated reaction was observed, indicating that the catalyst itself is causing significant decomposition. Titanocene dichloride proved ineffective in causing a reaction, and only starting material was recovered in reasonable yield. Attempting the chemistry of Njardarson[52] utilizing copper hexafluororacetoacetate once again resulted in decomposition, with the TLC profile and spectroscopic data matching the previous decomposition observed with allyl alcohol **122**. Of particular interest is that degredation studies of the substrates in acid or open to air produced identical reaction profiles, suggesting that acidic catalysts such as copper (II) hexafluoroacetoacetate are ill-suited for these substrates.

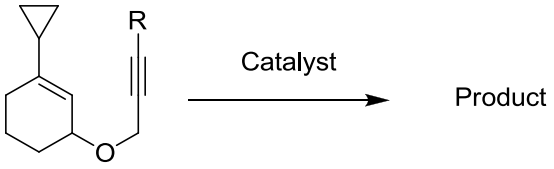
The likely cause for the rapid decomposition and difficult handling of the ether substrates stems from the electron-rich vinylcyclopropane moiety. It was determined that the substrates were much more stable in the absence of light based on TLC analysis, suggesting that the light-mediated decomposition of the vinylcyclopropane may have been a significant factor for these substrates. The substrates were stable for periods of several weeks at low temperatures in the absence of light and moisture, but would show significant decomposition after several hours at room temperature. Complicating the isolation and characterization of the products from the cycloaddition attempts was the fact that the products also appeared to be unstable for any period of time at room temperature. Mixture of isomers **139** proved to be the most stable, and was fully characterized, however low yields, instability of products and complicated spectra arising from mixtures of many isomers led to very difficult isolation and characterization of any additional products obtained from the cycloaddition reactions.

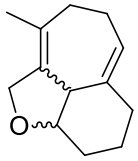
An additional problem encountered with the simple model substrates was that when the unsaturated carbon unit was not sterically congested, the reaction profile was complicated by the appearance of an additional major product appearing to result from transition-metal mediated “ene-yne” coupling, as evidenced by NMR, which clearly showed an intact cyclopropyl moiety and a large shift in the alkynyl or alkynyl methyl peak. The most successful reaction was with alkyne **113**, where the unsaturated carbon unit was sterically hindered enough to inhibit ene-yne coupling but not so hindered that the catalyst could not reach the alkyne, as was likely the case with the TMS-substituted alkyne, as evidenced by the extremely low yield and remaining starting material. This

particular reaction was difficult to isolate and purify, as the product once again proved unstable.

The low yield of the desired cycloaddition can be explained in a similar manner to the explanation provided by Hudlicky[3] in that the cyclopropyl ring would adopt a configuration that was not in conjugation with the cyclic olefin in order to minimize steric interactions with the cyclohexene moiety. In order to alleviate difficulties related to instability and volatility, and test whether a bulkier molecule could force the cyclopropyl ring into conjugation with the cyclohexene unit thereby facilitating the [5+2] reaction, a new series of model substrates were synthesized.

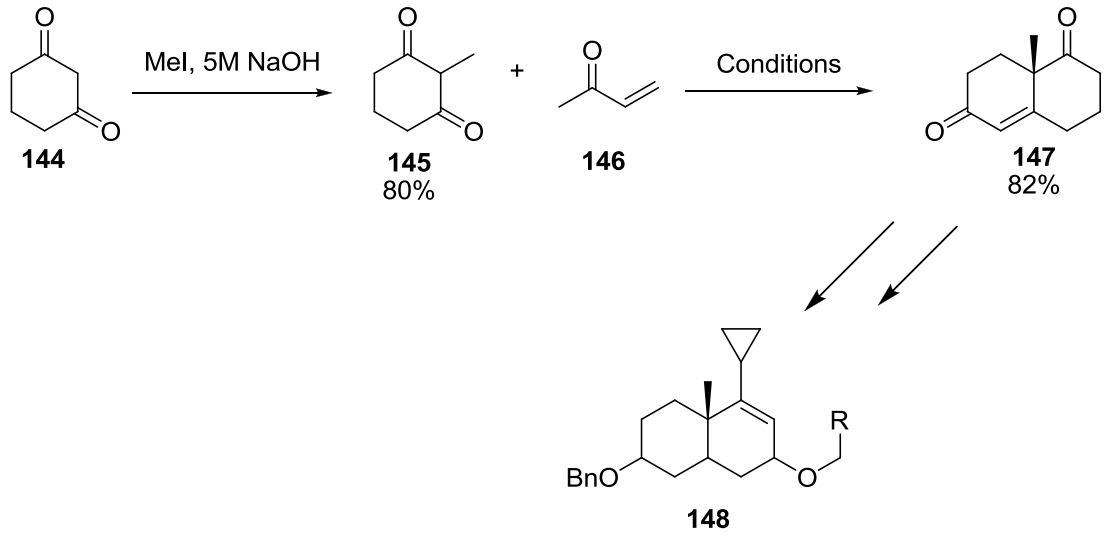
Table 4 – Catalyst Study on Alkynyl Ethers



Catalyst	Conditions	Result
3	R = Me, 1,2-DCE, 88 °C, sealed tube	 **139** 35%
90	R = Me, CH_2Cl_2, -30 °C – r.t.	N.R.
90	R = H, CH_2Cl_2, -30 °C – r.t.	N.R.
$Fe(CO)_5$	R = Me, IPA, UV irradiation, 1 atm. CO, Quartz vessel	Intractable mixture containing starting material as main component
$Fe(CO)_5$	R = H, IPA, UV irradiation, 1 atm. CO, Quartz vessel	Intractable mixture containing starting material as main component
Cp_2TiCl_2	R = Me, 1,2-DCE, 88 °C, Sealed Tube	N. R.
Cp_2TiCl_2	R = H, 1,2-DCE, 88 °C, sealed tube	N. R.
$Cu(hfacac)_2$	R = Me, Toluene, 150 °C, sealed vial	N. R.

3.4 – Synthesis of Bicyclic Substrates

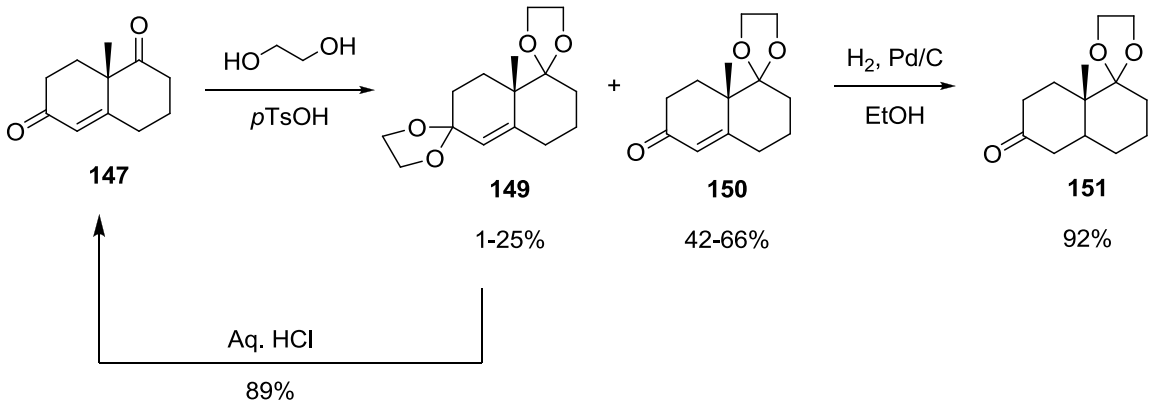
Owing to the volatility and instability of the simple model substrates, a change of model substrate was chosen. It was envisioned that a larger substrate with ancillary heteroatoms would provide less opportunity for the formation of a volatile product, and a more hindered molecule in general would be more stable to the reacting conditions and facilitate product isolation. The model substrate chosen was **148**, a substituted decalin with a benzyl ether for simple visualization by UV light.



Scheme 26 – Synthesis of Wieland-Miescher Ketone 147

The synthesis of the new substrate began with the methylation of 1,3-cyclohexadione **144** using methyl iodide, which proceeded without incident. Several conditions[53] are known for the Robinson annulation with methyl vinyl ketone **146**, which are outlined in detail in the experimental section. The use of hydroquinone and a proline

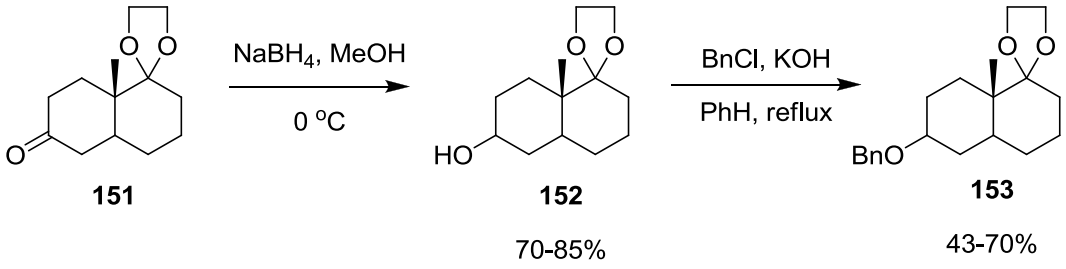
catalyst provided Wieland-Miescher ketone **147** in moderate yields, although with a reaction time of six days, whereas the use of KOH and piperidine afforded poor yields with a reaction time of several hours. Both procedures are well-suited to large-scale reactions.



Scheme 27 – Synthesis of Ketone 151

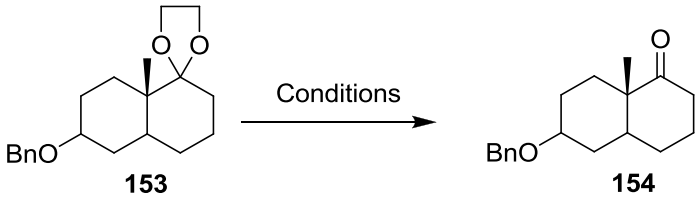
With **147** in hand in reasonable quantities, the selective protection of the ketone in the presence of the enone was attempted. Using a stoichiometric amount of freshly-crystallized *p*TsOH proved to be an important factor in the reaction.[54] Reportedly, under these conditions, the reaction should be complete in thirty minutes or less; however, longer reaction times of 2-3 hours proved more fruitful. As the ketone reacts much faster than the enone in this reaction, forcing a fast conversion by using stoichiometric acid causes a minimal amount of diketal **149**,[54] which is a common problem associated with selective protection of the Wieland-Miescher ketone. The amount of diketal produced could be controlled by using freshly-crystallized *p*TsOH, and what little could be

recovered from the reaction mixture usually persisted as a mixture with both starting material and the desired mono-ketal **150**. Subjecting this mixture to aqueous HCl cleavage conditions provided the starting ketone **147** in good yield, which upon purification could be again subjected to this reaction. The hydrogenation proceeded without incident, and crude reduced ketone **151** was sufficiently pure for subsequent transformation.



Scheme 28 – Formation of the Benzyl Ether 153

Reduction of ketone **151** to alcohol **152** proceeded in high yields. Benzyl protection provided benzyl acetal **153** in moderate yields, however occasional byproduct formation and recovery of starting material complicated the procedure. Large-scale experiments of this reaction worked well, provided the KOH was finely powdered and the reagents and solvent freshly-distilled.



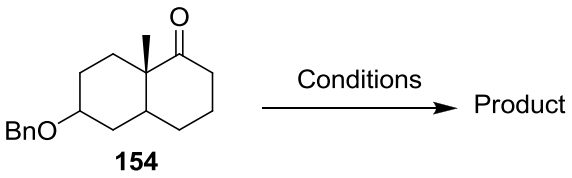
Scheme 29 – Deprotection of Ketal 153

The deprotection of ketal **153** was somewhat problematic. Initial experiments showed excellent conversion to ketone **154** with little to no side-reactions; scale-up procedures provided substantial amounts material in which both alcohol and ketone were deprotected, which unfortunately could not be transformed directly to ketone **154** without first protecting the alcohol. Initially, aqueous HCl was utilized, either neat or in methylene chloride, but it was found that the use of trifluoroacetic acid provided a much cleaner reaction, provided the reaction mixture was not too concentrated with respect to the acid. Standard yields of 60-70% were observed, as opposed to a wide range (30-80%) for the aqueous HCl reaction.

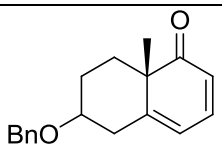
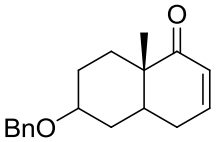
Many different conditions were attempted to oxidize ketone **154** into enone **155**, as outlined in the table below. Initial attempts centred on an α-bromination / debromination strategy, with mixed results, none of which formed the desired product. The use of bromine in acetic acid lead to a small amount of deprotected alcohol, but the reaction mixture was primarily starting material. The addition of a small amount of hydrobromic acid to the reaction caused near total consumption of starting material, giving rise to a complex mixture of products, none of which were the desired enone.

Bromine in methylene chloride caused consumption of starting material as well, and upon treatment with lithium chloride, diene **157** was recovered in moderate yields.

Table 5 – Oxidation of Ketone 154



154

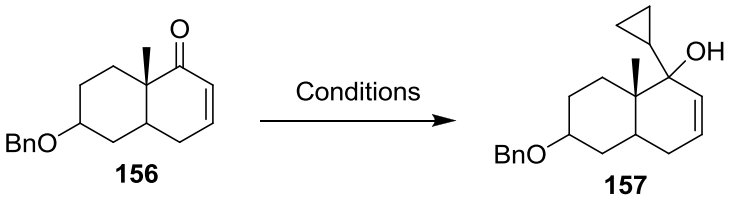
Conditions	Result
Br_2, AcOH, then $CaCO_3$	Loss of benzyl group, starting material
Br_2, HBr, AcOH then $CaCO_3$	Decomposition with small amounts of starting material
Br_2, HBr, AcOH then DBU	N.R.
Br_2, then Li_2CO_3	 **155**
NBS, Amberlyst-15	N.R.
*n*BuLi, TMSCl, then $Pd(OAc)_2$	 **156** 26%
*n*BuLi, TMSCl, then DDQ	N.R.
LDA, $(PhS)_2$, then *m*CPBA	**156**, 42%
LDA, $(PhSe)_2$, then H_2O_2	N.R.
LDA, PhSeBr, then H_2O_2	**156**, 40-50%
IBX	N.R.

Abandoning the bromination strategy, several other methodologies were employed. Saegusa oxidation proved somewhat successful when performed carefully with stoichiometric amounts of palladium (II) acetate, with the remainder being roughly

10% starting ketone and 60% TMS-enolate. The TMS-enolate was also stable to DDQ oxidation, which provided no reaction whatsoever. α-Thioether formation was relatively high-yielding, although the oxidation was complicated by byproducts resulting from overoxidation despite careful reaction monitoring and temperature control. Formation of an α-phenylselenide proved impossible when diphenyl diselenide was employed as electrophile, but the reaction did proceed when phenyl selenenyl bromide was used, which was formed immediately prior to use by the cleavage of diphenyl diselenide by bromine. Subsequent oxidation was very quick, and 40-50% of enone **156** was obtained regularly. Improvements on the yield have thus far not been possible, regardless of order of addition, temperature or solvent.

The Grignard reaction of enone **156** with cyclopropylmagnesium bromide was then studied in detail. Initial attempts at the reaction proved successful, with the yield ranging from 11-15%, with the majority of the remainder being unreacted starting material. **Table 6** tabulates the approaches to the formation of alcohol **157**.

Table 6 – Grignard Addition to Enone 156

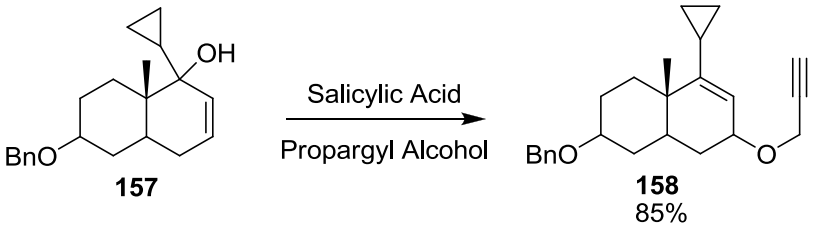


156 **157**

Condition	Result
156, Cyclopropylmagnesium Bromide, THF	15% **157**, 52% **156**
156, Cyclopropylmagnesium Bromide, Ether	11% **157**, 20% **156**
156, Cyclopropylmagnesium Bromide, $CeCl_3{*}7H_2O$, THF	N.R.
156, Cyclopropyllithium, Ether	9% **157**, 40% **156**
156, Cyclopropylmagnesium Bromide, $CeCl_3{*}2LiCl$, THF	12% **157**, 27% **156**

As can be seen from the above results, enone **156** is remarkably stable, and cannot be driven to completion through high temperatures or extra equivalents of incoming nucleophile; higher temperature causes further decomposition of the starting material, leading to poorer recovery, while additional equivalents of cyclopropyl nucleophile appear to have no effect. The most successful reaction thus far has been the standard Grignard reaction in refluxing THF, in which most of the starting material can be recovered. The use of a cerium salt stopped the reaction entirely, even after refluxing for three days, while cyclopropyllithium provided no benefits over the traditional Grignard. Knochel's THF-soluble lanthanide salt[55] was also attempted, with yields comparable to those of the Grignard reaction, although it does provide less recovered starting material, and the synthesis of the Knochel salt requires several days. The reason for this lack of reactivity remains unknown, however the electrophilic carbonyl carbon is quite sterically hindered by the angular methyl group as well as the fused bicyclic ring. To test this

hypothesis, a Luche reduction was employed on enone **156**, which provided 40% unreacted starting material, with the remainder appearing to be the reduced allyl alcohol.



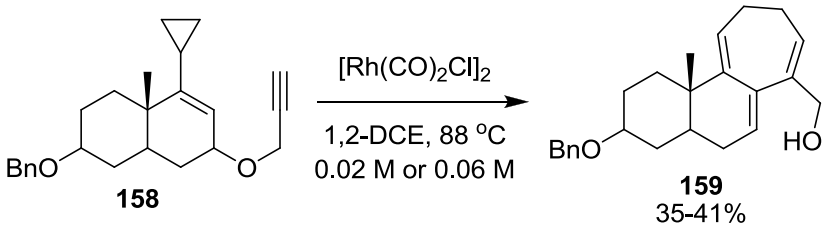
157 **158** 85%

Scheme 30 – Completion of Bicyclic Substrate

Following the Grignard reaction, acid-mediated allylic transposition worked quite well on small scale to provide the completed bicyclic substrate **158** in high yields.

3.5 – Cycloaddition Reactions of Bicyclic Substrates

Due to the significant bottleneck in the synthesis of bicyclic substrates, only one such compound has been tested to date for the [5+2] cycloaddition reaction. The reaction is outlined in **Scheme 32**.



Scheme 31 – [5+2] Cycloaddition of Bicylic Ether 158

The cycloaddition reaction proceeded smoothly, with a 41% yield at a dilution of 0.06M with respect to propargyl ether **158**. Somewhat surprisingly, the ether linkage appears to have eliminated during the course of the reaction after the [5+2] occurs. It is possible that the strain imposed by a tetracyclic framework renders the elimination spontaneous, but it could also be residual base from the base-wash preparation utilized for the sealed tube itself (see experimental section). Current studies are underway, but the facile nature of the cycloaddition itself is unexpected. If the previous attempts at forcing this reaction with different substrates were truly because of the cyclopropyl ring being out-of-plane with the olefin, perhaps vinyl ether **158** is locking the cyclopropyl ring in place through steric interactions, which would also explain the inherent lack of reactivity of the enone prior to the Grignard reaction. By TLC, the reaction profile appears to be mostly product and starting material. After three days the reaction did not seem to be progressing, even with the addition of more catalyst and prolonged heating. These

observations may suggest that one diastereomer of **158** reacts well, and the other may be blocked from reacting according to the geometry of the ring and benzyl group. Additional studies are needed to ascertain the reason for the lack of complete consumption of starting material after extended reaction times.

4. Conclusions and Future Work

The scope of the ring-constrained [5+2] cycloaddition reaction has been explored and somewhat expanded. The original hypothesis that the cyclohexadiene diol derivative could not undergo the cycloaddition due to sterics forcing the cyclopropyl ring out of planarity with respect to the olefin moiety seems plausible, as for small, unadorned ring-constrained vinylcyclopropanes, very few substrates were successful, and those that underwent the cycloaddition did so in very poor yields. Only when the substrate became more complex and sterically congested did the reaction proceed, and it is conceivable that having a *cis*-fused ring system could force the cyclopropane to adopt a more "conjugative" orientation with respect to the olefin, as could the angular methyl group at the ring junction. There remains a great deal of work to prove this theory, however.

Additional test reactions of the bicyclic substrates would help to illustrate exactly what the reasoning behind the limited substrate scope of the ring-constrained [5+2] cycloaddition. In order to streamline the synthesis of a library of test compounds, the oxidation to enone **156** would need to be studied in greater depth, and an alternative method for the addition of cyclopropyl Grignard reagents would need to be developed. Alternatively, a similar substrate could be synthesized without the ring junction methyl group to discern whether or not that has an effect on both these reactions and the cycloaddition itself. Finally, there are a wide number of ring-constrained vinylcyclopropanes that have not yet been tested, and alternative heteroatom or diester tethers could be used between the vinylcyclopropyl and alkene / alkyne moieties. Additional catalysts should also be attempted with these new substrates.

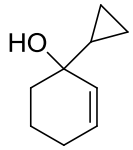
5. Experimental

General Experimental Details

All non-hydrolytic reactions were carried out under an argon atmosphere. Glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with argon. THF was distilled from potassium/benzophenone. Methylene chloride and acetonitrile were distilled from calcium hydride. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography was performed using silica gel 60-F254 plates. Melting points were measured on a Thomas-Hoover melting point apparatus and are reported uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR 1600 Series Spectrum One instrument and were recorded as a thin film on NaCl plates. ^{1}H and ^{l3}C NMR spectra were obtained on either a 300-MHz or 600 MHz Bruker instrument. Mass spectra were recorded on Kreatus/MsI Concept IS mass spectrometer at Brock University. Combustion analyses were performed by Atlantic Microlabs, Norcross, Georgia, USA.

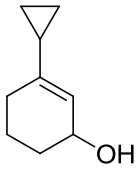
Standard conditions for the [5+2]-cycloaddition reaction

A base-washed (with a 1:1 MeOH : 10% NaOH solution) and oven-dried (12 h) sealed tube was charged with $[Rh(CO)_2Cl]_2$ (5 mol%) in distilled, degassed (N_2) 1,2-dichloroethane (0.1 M w.r.t. vinylcyclopropyl ether) before degassing the solution thoroughly once again. Vinylcyclopropyl ether was then added under nitrogen, and the tube was sealed behind a blast shield before placing in a pre-heated oil bath at 88^{o}C. Reaction progress was monitored by TLC. Upon completion, the mixture was filtered through a pad of celite (1:5 pentane : Et_2O), concentrated and purified by flash column chromatography.



1-cyclopropylcyclohex-2-enol 119

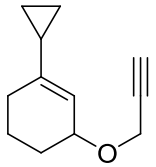
A 1-L flame-dried round-bottomed flask with attached reflux condenser was charged with magnesium turnings (3.75 g, 0.1545 mol). A crystal of iodine was added, and the flask heated under inert atmosphere. To this activated magnesium was added freshly-distilled tetrahydrofuran (500 mL), followed by bromocyclopropane (12.38 mL, 0.1545 mol). The mixture was heated to reflux and left for five hours. The reaction was then cooled to room temperature before cyclohexenone (10.0 mL, 0.1030 mol) was added dropwise before allowing the reaction to reflux overnight. After twelve hours, the mixture was cooled to room temperature and a saturated solution of ammonium chloride was added until the excess magnesium was dissolved. The solvent was evaporated in vacuo, and the aqueous residue extracted with dry diethyl ether (2 x 150 mL). Combined ethereal layers were rinsed with distilled water (25 mL) and brine (25 mL), then dried over sodium sulfate. Concentration gave **119** as a deep yellow oil (13.5 g, 0.0977 mol), used without further purification.



3-cyclopropylcyclohex-2-enol 122

To a stirred solution of alcohol **119** (2.3 g, 16.64 mmol) in a mixture of acetonitrile and distilled water (5:1 mixture, 66 mL) in a 250-mL round-bottomed flask was added salicylic acid (0.230 g, 1.664 mmol), and the mixture was allowed to stir overnight. Upon completion as monitored by TLC (9:1 Hexanes : Ethyl Acetate), a saturated solution of sodium bicarbonate was added (5 mL) and left to stir for 15 minutes. The mixture was concentrated to half volume and extracted with diethyl ether (3 x 70 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated to yield **122** as a yellow oil (2.57 g crude). The mixture was purified by flash column chromatography (20:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (1.89 g, 13.67 mmol, 82%).

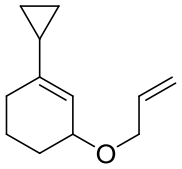
R_f = 0.25 (Hexanes : Ethyl acetate, 5:1); IR (KBr/ cm^{-1}): 3390, 3082, 3007, 2933, 1658, 1428, 1158, 1111, 1052, 1016, 974, 906, 817; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.50-5.49 (m, 1H), 4.16 (dd, J = 3.3, 1.3 Hz, 1H), 2.01-1.64 (m, 6H), 1.60-1.48 (m, 2H), 1.36-1.22 (m, 1H), 0.64-0.52 (m, 2H), 0.50-0.41 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.9, 122.2, 65.7, 32.1, 26.4, 19.0, 17.1, 4.9, 4.6 ppm; HRMS (+EI) calcd for $C_9H_{14}O$: 138.1045; found 138.1045.



1-cyclopropyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene 112

To a stirred solution of alcohol **119** (1.0 g, 7.235 mmol) in freshly-distilled acetonitrile (25 mL) in a flame-dried 250-mL round-bottomed flask was added salicylic acid (0.10 g, 0.7235 mmol) under an atmosphere of nitrogen at room temperature. Propargyl alcohol (4.2 mL, 72.35 mmol) was then added and the mixture was allowed to stir overnight. Upon completion as monitored by TLC (9:1 Hexanes : Ethyl Acetate), a saturated solution of sodium bicarbonate was added (5 mL) and left to stir for 15 minutes. The mixture was concentrated to half volume and extracted with diethyl ether (3 x 50mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated to yield **112** as a brown oil (11.78 g crude). The mixture was purified by flash column chromatography (20:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (0.566 g, 3.211 mmol, 44% over two steps).

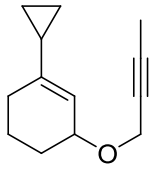
R_f = 0.60 (Hexanes : Ethyl acetate, 2:1); IR (KBr/ cm^{-1}): 3436, 3304, 3083, 3007, 2935, 2862, 2114, 1656, 1454, 1354, 1262, 1078, 1017, 901, 815, 623; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.54 (d, *J* = 3.3 Hz, 1H), 4.25-4.13 (m, 2H), 4.19 (t, *J* = 2.2 Hz, 2H), 4.07 (t, *J* = 2.6 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H), 1.94-1.50 (m, 7H), 1.39-1.26 (m, 1H), 0.62-0.54 (m, 2H), 0.54-0.46 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.0, 119.2, 80.6, 73.7, 72.2, 55.1, 28.1, 26.6, 19.1, 17.2, 4.9, 4.7 ppm; HRMS (+EI) calcd for $C_{12}H_{16}O$: 176.1201; found 176.1204; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15; Found: C, 81.74; H, 9.29.



3-(allyloxy)-1-cyclopropylcyclohex-1-ene 115

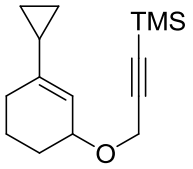
To a stirred solution of alcohol **119** (0.500 g, 3.618 mmol) in freshly-distilled acetonitrile (12 mL) in a flame-dried 100-mL round-bottomed flask was added salicylic acid (0.050 g, 0.3618 mmol) under an atmosphere of nitrogen at room temperature. Allyl alcohol (2.5 mL, 36.18 mmol) was then added and the mixture was allowed to stir overnight. Upon completion as monitored by TLC (9:1 Hexanes : Ethyl Acetate), a saturated solution of sodium bicarbonate was added (5 mL) and left to stir for 15 minutes. The mixture was concentrated to half volume and extracted with diethyl ether (4 x 25 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated to yield **115** as a slightly yellow oil (512 mg crude). The mixture was purified by flash column chromatography (20:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (0.497 g, 2.788 mmol, 77%).

R_f = 0.53 (Hexanes: Ethyl acetate, 9:1); IR (KBr/ cm^{-1}): 3340, 3082, 3005, 2934, 2862, 2236, 1722, 1657, 1454, 1423, 1333, 1259, 1075, 919, 814, 754, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.94 (ddt, *J* = 17.2, 10.6, 5.6, 1H), 5.53 (d, *J* = 2.6, 1H), 5.27 (dd, *J* = 17.2, 1.7, 1H), 5.15 (dd, *J* = 10.3, 1.6, 1H), 4.02 (tt, *J* = 3.8, 2.4, 2H), 3.89 (d, *J* = 3.1, 1H), 1.94-1.69 (m, 4H), 1.68-1.46 (m, 2H), 1.39-1.27 (m, 1H), 0.61-0.54 (m, 2H), 0.52-0.42 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.9, 135.5, 120.1, 116.2, 72.5, 69.0, 28.4, 26.5, 19.2, 17.1, 4.6, 4.5 ppm. Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18; Found: C, 81.10; H, 10.45.



3-(but-2-yn-1-yloxy)-1-cyclopropylcyclohex-1-ene 113

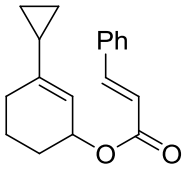
To a stirred solution of alkyne **112** (0.364 g, 2.06 mmol) in freshly-distilled THF (7 mL) in a flame-dried 100-mL round-bottomed flask at 0 ^{o}C was added *n*-butyllithium solution (0.94 mL, 2.2 M, 2.06 mmol) over a ten-minute period under an atmosphere of nitrogen. The reaction was allowed to slowly warm to room temperature before methyl iodide (0.2 mL, 3.09 mmol) was added in one portion and the reaction left to stir overnight. The reaction was then quenched with saturated ammonium chloride (5 mL) and diluted with diethyl ether (30 mL). The organic layer was washed with water (10 mL), saturated sodium thiosulfate (10 mL), and brine (10 mL). The ethereal layer was then dried with magnesium sulfate, filtered, and concentrated *in vacuo* to yield **113** as a slight yellow oil. The mixture was purified by flash column chromatography (10:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (0.326 g, 83 %). R_f = 0.51 (Hexane : Ethyl Acetate, 3:1); IR (Thin Film) 3082, 3006, 2934, 2860, 1658, 1450, 1354, 1261, 1134, 1074, 947, 906, 816 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.55 (d, J = 3.0 Hz, 1H), 4.20-4.09 (m, 2H), 4.04 (d, J = 2.8 Hz, 1H), 1.93-1.81 (m, 3H), 1.81-1.50 (m, 6H), 1.34 (tt, J = 8.9, 4.7 Hz, 1H), 0.62-0.54 (m, 2H), 0.54-0.46 (m, 2H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$): δ 143.7, 119.5, 81.8, 75.8, 72.0, 55.7, 28.1, 26.6, 19.2, 17.2, 4.8, 4.7, 3.7 ppm; HRMS calcd for $C_{13}H_{18}O$: 190.1362, Found: 190.1358.



(3-(3-cyclopropylcyclohex-2-enyloxy)prop-1-ynyl)trimethylsilane 114

To a stirred solution of alkyne **112** (0.218 g, 1.24 mmol) in freshly-distilled THF (10 mL) in a flame-dried 25-mL round-bottomed flask at -78 ^{o}C was added *n*-butyllithium solution (0.59 mL, 2.3 M, 1.36 mmol) over a ten-minute period under an atmosphere of nitrogen. The reaction was allowed to stir for twenty minutes before chlorotrimethylsilane (0.24 mL, 1.86 mmol) was added in one portion and the reaction left to stir overnight. The reaction was then quenched with distilled water (5 mL) and 1 M HCl (3 mL), and the aqueous residue extracted with diethyl ether (3 x 30 mL). The organic layer was washed with brine (10 mL), then dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield **114** as a slightly yellow oil. The mixture was purified by flash column chromatography (20:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (0.249 g, , 1.00 mmol, 81 %).

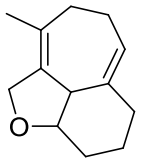
R_f = 0.63 (Hexane : Ethyl Acetate, 9:1); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.54 (d, J = 3.1 Hz, 1H), 4.18 (d, J = 3.2 Hz, 2H), 4.08-4.01 (m, 1H), 1.94-1.61 (m, 5H), 1.59-1.46 (m, 1H), 1.33 (tt, J = 8.3, 5.4 Hz, 1H), 0.61-0.54 (m, 2H), 0.51-0.44 (m, 2H), 0.17 (s, 9H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$): δ 144.0, 119.7, 102.7, 90.7, 72.5, 56.2, 28.2, 26.7, 19.3, 17.4, 5.0, 4.8, 0.0 ppm.



3-cyclopropylcyclohex-2-enyl cinnamate 136

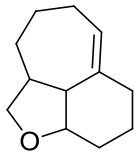
To a stirred solution of alcohol **119** (0.200 g, 1.45 mmol) in freshly-distilled acetonitrile (15 mL) in a flame-dried 25-mL round-bottomed flask was added cinnamic acid (2.14 g, 14.5 mmol) under an atmosphere of nitrogen at room temperature and the mixture was allowed to stir overnight. Upon completion as monitored by TLC (4:1 Hexanes : Ethyl Acetate), the reaction mixture was filtered to remove undissolved cinnamic acid and diluted with 50 mL diethyl ether. The ethereal solution was rinsed with sat. sodium bicarbonate (3 x 10 mL), and the combined aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated to yield **136** as a slightly yellow oil. The mixture was purified by flash column chromatography (15:1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (0.202 g, 0.752 mmol, 52%).

R_f = 0.59 (Hexane : Ethyl Acetate, 4:1); IR (Thin Film) 3076, 3021, 3005, 2934, 2857, 1659, 1596, 1577, 1495, 1448, 1380, 1330, 1204, 1157, 1111, 1072, 963, 905, 814, 735, 691 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 7.41 (d, J = 8.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.28-7.22 (m, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.34 (dt, J = 15.9, 6.0 Hz, 1H), 5.60 (d, J = 2.9 Hz, 1H), 4.21 (td, J = 3.0, 1.3 Hz, 2H), 4.00-3.95 (m, 1H), 1.85-1.75 (m, 3H), 1.63-1.52 (m, 1H), 1.42-1.32 (m, 1H), 0.65-0.58 (m, 2H), 0.55-0.49 (m, 2H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$): δ 143.3, 136.9, 131.8, 128.5, 127.5, 127.0, 126.5, 120.1, 72.7, 68.7, 28.5, 26.5, 19.3, 17.3, 4.8, 4.6 ppm.



3-methyl-2,2a[1],4,5,7,8,9,9a-octahydrocyclohepta[*cd*]benzofuran 139

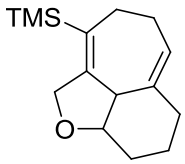
A base-washed (with a 1:1 MeOH : 10% NaOH solution) and oven-dried (12 h) 25-mL sealed tube was charged with $[Rh(CO)_2Cl]_2$ (0.02 g, 0.053 mmol) in distilled, degassed (Ar) 1,2-dichloroethane (5 mL) before degassing the solution thoroughly once again. Ether **113** (0.101 g, 0.525 mmol) was then added under argon, and the tube was sealed behind a blast shield before placing in a pre-heated oil bath at 88°C. The reaction was left to stir for 1 h, and was then filtered through silica (Ethyl Acetate) and concentrated to provide a dark brown oil. The crude mixture was purified by flash column chromatography (15:1 Hexanes : Ethyl Acetate) to provide **139** as a colourless oil. R_f = 0.52 (Hexane : Ethyl Acetate, 6:1); IR (Thin Film) 2935, 2863, 1723, 1651, 1431, 1367, 1046, 925, 845, 757, 664 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 5.37-5.34 (m. 1H), 4.51-4.45 (m, 1H), 4.22-4.17 (m, 1H), 4.13-4.07 (m, 1H), 3.73-3.68 (m, 1H), 2.63-2.52 (m, 1H), 2.29-2.09 (m, 4H), 2.01-1.75 (m, 2H), 1.71-1.60 (m, 4H), 1.53-1.39 (m, 1H), 1.35-1.18 (m, 1H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$): δ 137.5, 136.8, 126.9, 124.7, 78.6, 69.4, 42.4, 34.2, 31.9, 28.2, 25.7, 20.4, 19.8 ppm; HRMS calcd for $C_{13}H_{18}O$: 190.1362, Found: 190.1358; Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53; Found: C, 81.88; H, 9.48.



2,2a[1],3[1], 4[1], 4,5,7,8,9,9a-decahydrocyclohepta[*cd*]benzofuran 141

A base-washed (with a 1:1 MeOH : 10% NaOH solution) and oven-dried (12 h) 25-mL sealed tube was charged with $[Rh(CO)_2Cl]_2$ (0.017 g, 0.048 mmol) in distilled, degassed (Ar) 1,2-dichloroethane (10 mL) before degassing the solution thoroughly once again. Ether **115** (0.171 g, 0.959 mmol) was then added under argon, and the tube was sealed behind a blast shield before placing in a pre-heated oil bath at 88°C. The reaction was left to stir for 3 days, filtered through a pad of celite (1:5 pentane : Et_2O), concentrated and purified by flash column chromatography on deactivated silica (10% H_2O) (20:1 Hexanes : Ethyl Acetate) to provide **141** as a colourless oil (78 mg, 0.438 mmol, 46%).

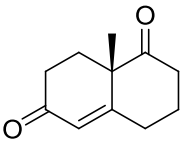
R_f = 0.49 (Hexane : Ethyl Acetate, 9:1); ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.64 (dt, *J* = 21.2, 8.4 Hz, 1H), 6.03 (d, *J* = 11.0 Hz, 1H), 5.15 (d, *J* = 15.8 Hz, 1H), 5.02 (d, *J* = 10.7 Hz, 1H), 4.17 (t, *J* = 8.2 Hz, 1H), 4.07 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.44 (t, *J* = 8.8 Hz, 1H), 2.97 (dd, *J* = 11.2, 7.2 Hz, 1H), 2.47-2.26 (m, 2H), 2.24-2.02 (m, 3H), 1.78-1.67 (m, 2H), 1.49-1.18 (m, 3H) ppm.



3-(trimethyl)silyl-2,2a[1],4,5,7,8,9,9a-octahydrocyclohepta[*cd*]benzofuran 140

A base-washed (with a 1:1 MeOH : 10% NaOH solution) and oven-dried (12 h) 25-mL sealed tube was charged with $[Rh(CO)_2Cl]_2$ (0.007 g, 0.017 mmol) in distilled, degassed (Ar) 1,2-dichloroethane (3 mL) before degassing the solution thoroughly once again. Ether **114** (0.083 g, 0.33 mmol) was then added under argon, and the tube was sealed behind a blast shield before placing in a pre-heated oil bath at 88°C. The reaction was left to stir for 3 h, filtered through a pad of celite (1:5 pentane : Et_2O), and concentrated to give a brown oil (95 mg). The crude mixture was purified by flash column chromatography on deactivated silica (10% w/w H_2O) (20:1 Pentane : Diethyl Ether) to provide **140** as a colourless oil (2 mg, 0.008 mmol, 2%).

R_f = 0.35 (15:1, Pentane : Diethyl Ether); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.62-5.56 (m, 1H), 4.46 (d, J = 13.5 Hz, 1H), 4.30 (dt, J = 13.4, 2.5 Hz, 1H), 3.15 (td, J = 5.5, 3.6 Hz, 1H), 2.90-2.80 (m, 1H), 2.16-2.07 (m, 3H), 0.62-0.45 (m, 2H), 0.42-0.35 (m, 2H), 0.19-0.14 (m, 3H), 0.10 (s, 9H) ppm.



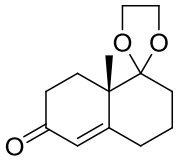
8a-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione 147

Using piperidine:[56]

A flame-dried, argon-purged 25-mL round-bottomed flask was charged with 2-methylcyclohexane-1,3-dione **145** (240 mg, 1.90 mmol) dissolved in distilled methanol (10 mL). Methyl vinyl ketone **146** (234 μL, 2.85 mmol) was added at room temperature, followed by a catalytic amount of powdered potassium hydroxide. The reaction vessel was fitted with a reflux condenser and the reaction heated to reflux. After 3 hours, the solvent and excess methyl vinyl ketone was removed via distillation under reduced pressure before resuspending the resulting residue in distilled benzene (10 mL). The reaction flask was fitted with a Dean-Starke apparatus, and the first 2 mL of solution collected was removed to ensure complete removal of excess methyl vinyl ketone. The reaction was allowed to cool to room temperature before piperidine was added (19 μL, 0.19 mmol) and the reaction heated to reflux. After 45 minutes, the solvent was removed via distillation and the reaction vessel left to cool to room temperature before dilution with diethyl ether (10 mL). The organic residue was rinsed with 4 mL 0.5M HCl solution, then 4 mL distilled water. The combined aqueous layers were extracted 2x 10 mL diethyl ether, and combined organic layers rinsed with 3x 10 mL distilled water, 10 mL brine and dried over $MgSO_4$. The ethereal layer was filtered and concentrated to provide **147** as a purple oil. The product was purified via flash column chromatography (2 : 1 Hexanes : Ethyl Acetate) to provide pure **147** as a colourless oil (76 mg, 0.43 mmol, 22%, 2 steps).

Using proline:[57]

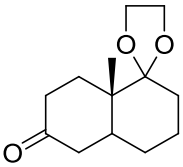
A 25-mL round-bottomed flask was charged with 2-methylcyclohexane-1,3-dione **145** (1.329 g, 10.53 mmol) dissolved in distilled water (5 mL). Hydroquinone (12 mg, 0.11 mmol) was added at room temperature, followed by methyl vinyl ketone **146** (1.73 mL, 21.07 mmol). The reaction was then heated to 75 ^{o}C. After 4 hours, the solution was concentrated under reduced pressure and the resulting brown oil dissolved in distilled DMSO (6 mL) before degassing with nitrogen. A catalytic amount of (L)-Proline was added, and the reaction allowed to stir at room temperature under an atmosphere of nitrogen for 6 days. The reaction was diluted with distilled water (10 mL), and the aqueous residue extracted 3x 10 mL ethyl acetate. The combined organic layers were rinsed with 5 mL distilled water, 5 mL brine and dried over sodium sulfate to provide **147** as a brown oil. The product was purified via flash column chromatography (2 : 1 Hexanes : Ethyl Acetate) to afford pure **147** as a colourless oil (1.53 g, 81%). R_f = 0.43 (Hexanes: Ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.79 (d, *J* = 1.83 Hz, 1H), 2.74-2.59 (m, 2H), 2.50-2.34 (m, 4H), 2.15-2.03 (m, 3H), 1.65 (qt, *J* = 13.30, 4.46, 1H), 1.39 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.1, 198.4, 165.9, 125.9, 50.7, 37.8, 33.7, 31.9, 29.8, 23.4, 23.0 ppm



8a'-methyl-3',4',8',8a'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one
150

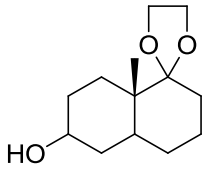
A flame-dried 250-mL round-bottomed flask containing activated 4 A molecular sieves was charged with Wieland-Miescher ketone **147** (2.8 g, 15.71 mmol) dissolved in freshly-distilled ethylene glycol (100 mL) under an atmosphere of nitrogen. *Para*-Toluenesulfonic acid (3.0 g, 15.71 mmol) was added and the mixture was allowed to stir at room temperature for 3 hours. The reaction was then decanted into a saturated solution of sodium bicarbonate containing ice (300 mL), and the aqueous solution extracted 3x 150 mL ethyl acetate. The combined organic layers were rinsed with brine (40 mL) and dried over magnesium sulfate to provide 8a'-methyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one **150** as a dark yellow oil. The product was purified via flash column chromatography (4 : 1 Hexanes : Ethyl Acetate) to provide pure **150** as a colourless oil (2.32 g, 10.44 mmol, 66%).

R_f = 0.55 (Hexanes: Ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.80 (d, J = 1.89 Hz, 1H), 3.97-3.89 (m, 4H), 2.43-2.13 (m, 4H), 1.81-1.59 (m, 6H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.3, 167.8, 125.7, 112.5, 65.5, 65.2, 45.1, 34.0, 31.5, 30.2, 26.9, 21.8, 20.6 ppm.



8a'-methylhexahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one 151

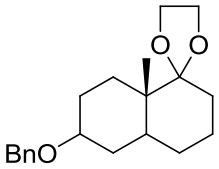
A 100-mL round-bottomed flask was charged with enone **150** (711 mg, 3.20 mmol) dissolved in absolute ethanol (35 mL). A catalytic amount of palladium on activated carbon (10% w/w) was added, and the flask purged with hydrogen. The reaction was stirred under an atmosphere of hydrogen for 3.5 hours before being filtered through a plug of silica with absolute ethanol. The ethanolic solution was concentrated to provide **151** (669 mg, 2.98 mmol, 93%) as a slight yellow oil, used without further purification. $R_f = 0.51$ (Hexanes: Ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99-3.87 (m, 4H), 2.62 (dd, J = 14.90, 5.90 Hz, 1H), 2.49-2.25 (m, 2H), 2.21-2.04 (m, 3H), 1.81-1.70 (m, 2H), 1.69-1.44 (m, 4H), 1.30-1.24 (m, 1H), 1.19 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.5, 112.6, 65.2, 65.1, 44.3, 42.8, 41.4, 38.0, 29.8, 29.2, 28.4, 22.4, 17.8 ppm.



8a'-methyloctahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'-ol 152

A flame-dried 100-mL round-bottomed flask was charged with ketone **151** (669 mg, 2.98 mmol) dissolved in distilled methanol (30 mL) under an atmosphere of nitrogen. The flask was cooled to 0 ^{o}C before sodium borohydride (90 mg, 2.386 mmol) was added in one portion, and the solution left to stir at 0 ^{o}C overnight. The solvent was removed under reduced pressure, and the organic residue resuspended in distilled water (10 mL). The aqueous solution was extracted 3x 30 mL benzene, and the combined organic layers were rinsed with 10 mL brine and dried over sodium sulfate to provide **152** as a slight yellow oil. The product was purified via flash column chromatography (2 : 1 Hexanes : Ethyl Acetate) and isolated as a colourless oil (660 mg, 2.92 mmol, 97 %).

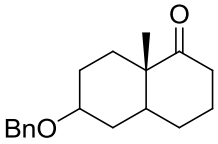
R_f = 0.7 (Hexanes: Ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.98-3.83 (m, 4H), 3.72 (bs, 1H), 2.00 (dt, *J* = 14.32, 4.97 Hz, 1H), 1.78-1.67 (m, 4H), 1.61-1.53 (m, 5H), 1.52-1.41 (m, 3H), 1.01 (s, 3H), 1.00-0.98 (m, 1H) ppm.



6'-(benzyloxy)-8a'-methyloctahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalene] 153

A flame-dried 100-mL round-bottomed flask was charged with alcohol **152** (448 mg, 1.98 mmol) dissolved in freshly-distilled benzene (30 mL) under an atmosphere of argon. Distilled benzyl chloride (911 μL, 7.92 mmol) was then added, followed by powdered potassium hydroxide (1.11 g, 19.79 mmol) and the mixture was heated to reflux overnight. The reaction was then filtered to remove excess potassium hydroxide and concentrated to provide **153** as a light yellow oil. The product was purified via flash column chromatography (9 : 1 Hexanes : Ethyl Acetate) to yield **153** as a slightly yellow oil (212 mg, 0.67 mmol, 34%).

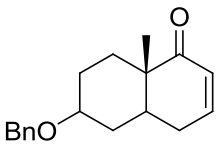
R_f = 0.62 (Hexanes: Ethyl acetate, 4:1); IR (KBr/ cm^{-1}): 3087, 3063, 3029, 2929, 2867, 2672, 2245, 1949, 1870, 1808, 1740, 1705, 1606, 1586, 1495, 1452, 1381, 1358, 1335, 1297, 1270, 1225, 1198, 1171, 1116, 1089, 1068, 1035, 987, 951, 908, 841, 733, 697, 646, 598; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.22 (m, 5H), 4.54 (dd, *J* = 18.26, 12.17 Hz, 2H), 4.00-3.85 (m, 5H), 3.52-3.41 (m, 1H), 2.07-1.90 (m, 2H), 1.88-1.45 (m, 10H), 1.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.5, 128.4, 127.6, 127.3, 113.5, 69.9, 64.5, 64.3, 63.7, 31.2, 29.2 ppm; HRMS (+EI) calcd for $C_{18}H_{24}O_2$: 316.2038; found 316.2044.



6-(benzyloxy)-8a-methyloctahydronaphthalen-1(2*H*)-one 154

A 250-mL round-bottomed flask was charged with ketal **153** (562 mg, 1.78 mmol) dissolved in distilled methanol (25 mL) at room temperature. Trifluoroacetic acid (5 mL) was then added dropwise over 10 minutes, and the resulting solution allowed to stir for 2 hours. The reaction was then concentrated and excess trifluoroacetic acid removed as an azeotrope with toluene to provide **154** as a light yellow oil. The product was purified via flash column chromatography (9 : 1 Hexanes : Ethyl Acetate) to yield pure **154** as a colourless oil (291 mg, 1.07 mmol, 60%).

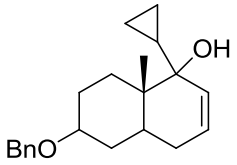
R_f = 0.53 (Hexanes: Ethyl acetate, 4:1); IR (KBr/ cm^{-1}): 3063, 3029, 2937, 2868, 1704, 1496, 1453, 1424, 1378, 1361, 1311, 1231, 1140, 1096, 1070, 1028, 976, 823, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.23 (m, 5H), 4.53 (dd, *J* = 17.63, 11.87 Hz, 2H), 3.36 (tt, *J* = 10.81, 3.98 Hz, 1H), 2.61-2.46 (m, 1H), 2.32 (dt, *J* = 13.94, 3.77 Hz, 1H), 2.27-2.13 (m, 2H), 2.06-1.72 (m, 5H), 1.55-1.33 (m, 3H), 1.19 (s, 3H), 0.87 (td, *J* = 6.81, 3.94 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.8, 139.1, 128.4, 127.6, 127.4, 76.7, 48.9, 43.6, 37.8, 35.4, 33.9, 32.9, 30.9, 29.2, 27.6, 26.5, 22.1 ppm; HRMS (+EI) calcd for $C_{18}H_{24}O_2$: 272.1776; found 272.1779; Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88; Found: C, 79.23; H, 8.83.



6-(benzyloxy)-8a-methyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4*H*)-one 156

A 150-mL flame-dried round-bottomed flask under an atmosphere of argon was charged with diisopropylamine (2.67 μL, 1.892 mmol) dissolved in freshly-distilled THF (6 mL) and cooled to -78 ^{o}C before *n*-butyllithium was added (2.20 M, 0.72 mL) dropwise over 5 minutes. The resulting solution was allowed to stir for 40 minutes. In a separate 25-mL flame-dried round-bottomed flask was dissolved **155** in freshly-distilled THF (6 mL) and added dropwise *via* syringe to the butyllithium solution at -78 ^{o}C and the solution allowed to stir for 25 minutes. Freshly-prepared phenylselenenyl bromide in 5 mL freshly-distilled THF was then added in one portion at -78 ^{o}C and allowed to warm to room temperature. The reaction was then poured into 20 mL of 0.5N HCl and 120 mL Et_2O. The organic layer was rinsed with 10 mL sat. sodium bicarbonate solution and 10 mL brine, then dried over magnesium sulfate, filtered and concentrated to give the crude *a*-phenylselenide as a yellow oil. The oil was resuspended in 15 mL THF and cooled to 0 ^{o}C before H_2O_2 (30% aqueous, 1.5 mL) was added dropwise until the vibrant yellow colour disappeared. The mixture was then allowed to warm to room temperature. It was then diluted with 50 mL Et_2O and rinsed with 5 mL distilled H_2O, 5 mL saturated sodium carbonate solution. The ethereal layer was then dried over magnesium sulfate, filtered and concentrated to provide **156** as a slight yellow oil. It was further purified *via* flash column chromatography (9 : 1 Hex : EtOAc) and isolated as a colourless oil (186 mg, 0.6879 mmol, 44% over 2 steps).

R_f = 0.41 (Hexanes: Ethyl acetate, 4:1); IR (KBr/ cm^{-1}): 3063, 3031, 2935, 2868, 1673, 1625, 1454, 1427, 1388, 1361, 1231, 1211, 1129, 1120, 1097, 1074, 1027, 912, 810, 734, 698, 649; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.23 (m, 5H), 4.53 (dd, *J* = 17.63, 11.87 Hz, 2H), 3.36 (tt, *J* = 10.81, 3.98 Hz, 1H), 2.61-2.46 (m, 1H), 2.32 (dt, *J* = 13.94, 3.77 Hz, 1H), 2.27-2.13 (m, 2H), 2.06-1.72 (m, 5H), 1.55-1.33 (m, 3H), 1.19 (s, 3H), 0.87 (td, *J* = 6.81, 3.94 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.97, 145.94, 139.10, 128.49, 127.93, 127.70, 127.61, 127.55, 76.74, 69.88, 46.27, 40.99, 35.63, 32.64, 30.21, 29.40, 27.78, 24.78 ppm; HRMS (+EI) calcd for $C_{18}H_{22}O_2$: 270.1620; found 270.1618; Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; Found: C, 79.83; H, 7.97.

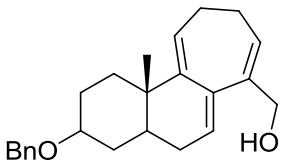


6-(benzyloxy)-1-cyclopropyl-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol 157

A 25-mL flame-dried round-bottomed flask with attached reflux condenser was charged with magnesium turnings (0.025 g, 1.03 mmol). A crystal of iodine was added, and the flask heated under inert atmosphere. To this activated magnesium was added freshly-distilled tetrahydrofuran (3 mL), followed by bromocyclopropane (0.083 mL, 1.03 mmol). The mixture was heated to reflux and left for three hours. The reaction was then cooled to room temperature before enone **156** (0.186 g, 0.688 mmol) in freshly-distilled tetrahydrofuran (5 mL) was added dropwise before allowing the reaction to reflux overnight. After twelve hours, the mixture was cooled to room temperature and a saturated solution of ammonium chloride (2 mL) was added until the excess magnesium was dissolved. The solvent was evaporated *in vacuo*, and the aqueous residue extracted with diethyl ether (3 x 25 mL). Combined ethereal layers were rinsed with distilled water (5 mL) and brine (5 mL), then dried over magnesium sulfate. Concentration gave **157** as a deep yellow oil (128 mg). The crude reaction mixture was purified *via* flash column chromatography (9:1 Hexanes : Ethyl Acetate) to provide alcohol **157** as a colourless oil (32 mg, 0.102 mmol, 15%).

R_f = 0.60 (Hexanes: Ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.23 (m, 5H), 5.68 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 4.53 (s, 2H), 3.62-3.56 (m, 1H), 2.16-2.01 (m, 2H), 1.99-1.81 (m, 3H), 1.79-1.67 (m, 3H), 1.29-1.21 (m, 2H), 1.06 (s, 3H),

0.56-0.23 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.5, 129.1, 128.5, 128.4, 127.6, 127.4, 127.3, 76.2, 74.0, 69.8, 39.4, 37.7, 33.9, 32.9, 29.4, 28.1, 18.1, 1.2, 0.3 ppm.

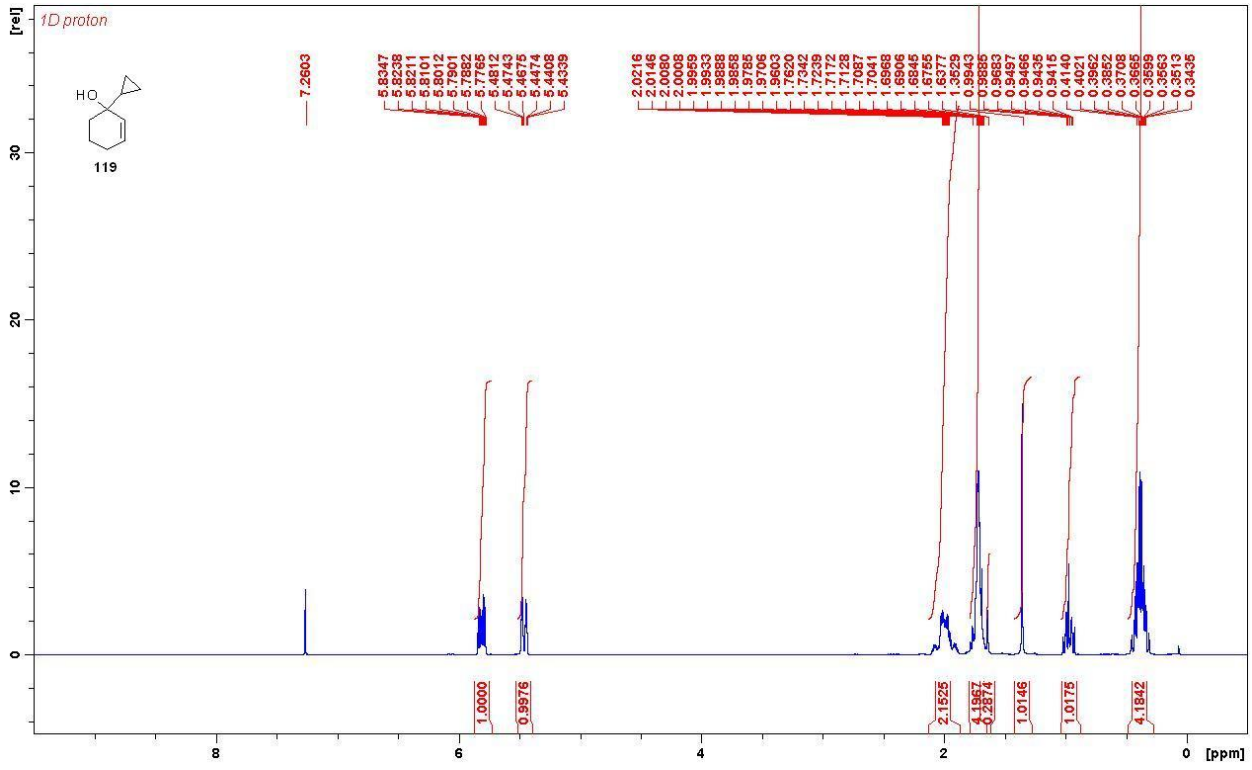


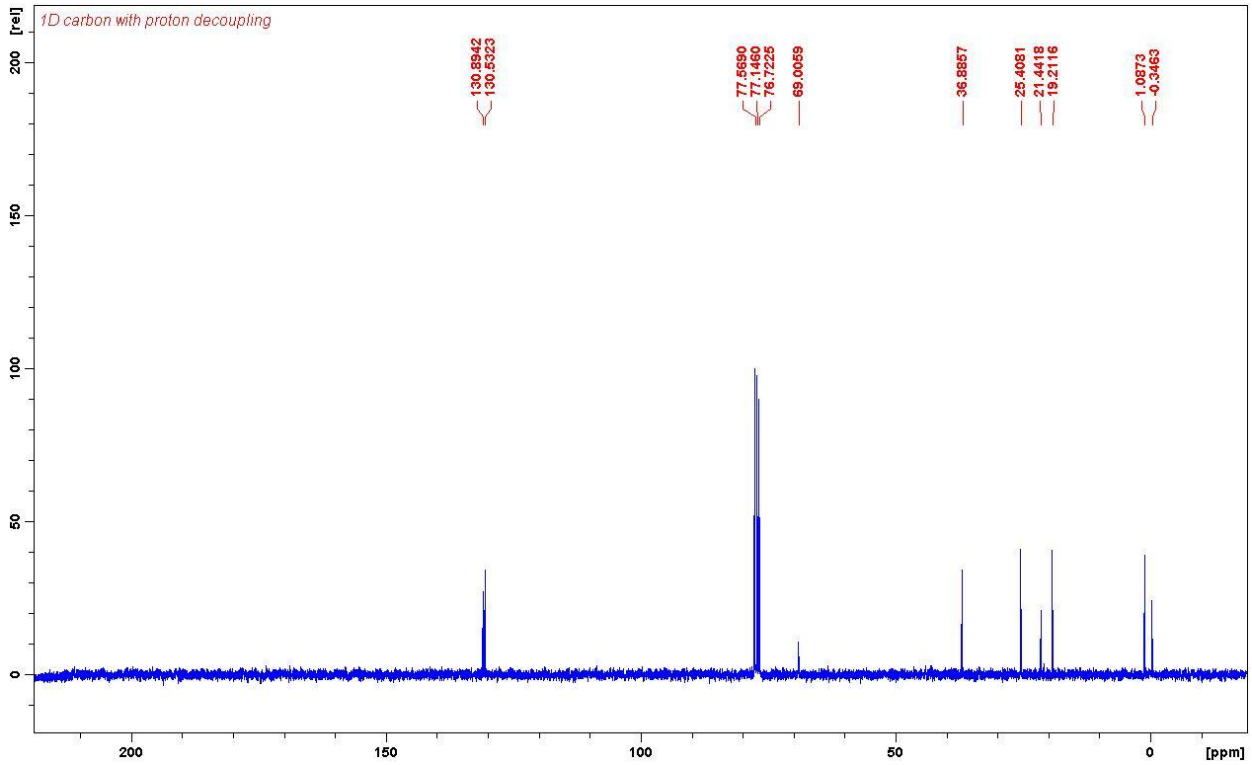
(3-(benzyloxy)-11b-methyl-2,3,4,4a,5,9,10,11b-octahydro-1*H*-cyclohepta[*a*]naphthalen-7-yl)methanol 159

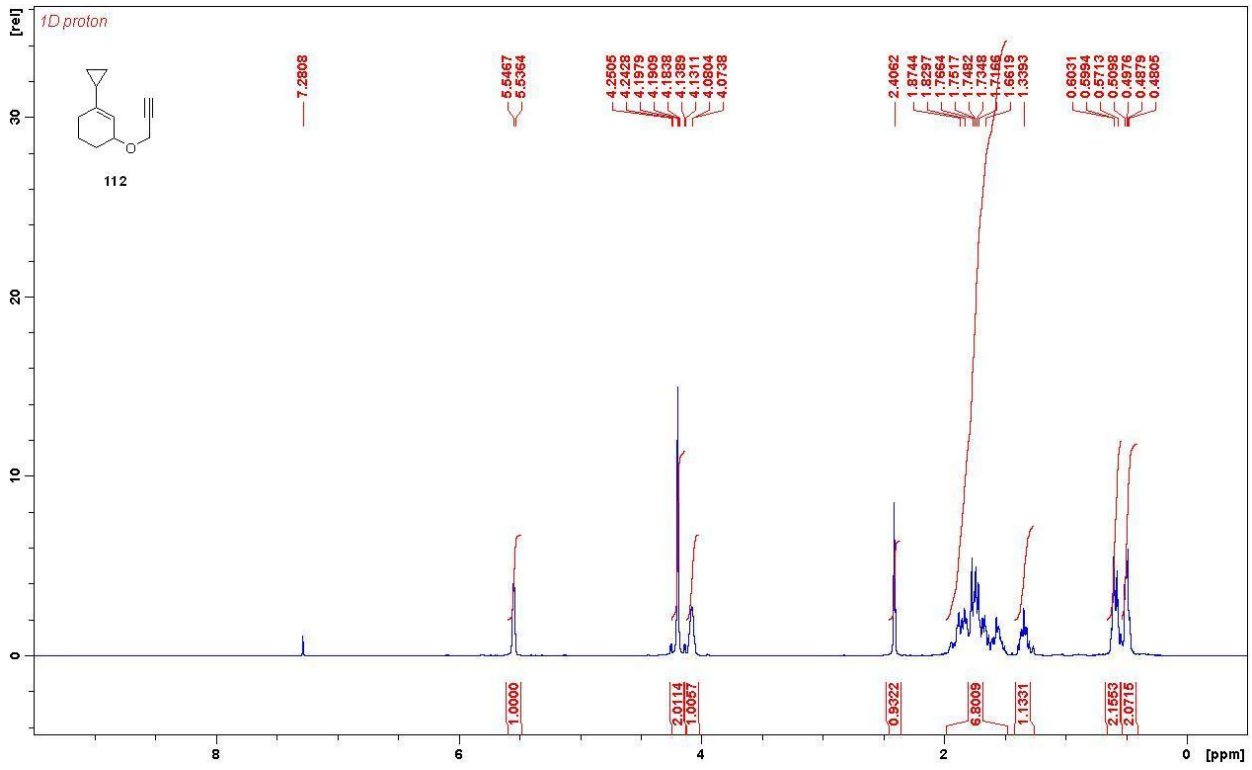
A base-washed (with a 1:1 MeOH : 10% NaOH solution) and oven-dried (12 h) 25-mL sealed tube was charged with $[Rh(CO)_2Cl]_2$ (spatula tip) in distilled, degassed (Ar) 1,2-dichloroethane (1 mL) before degassing the solution thoroughly once again. Ether **158** (0.022 g, 0.063 mmol) was then added under argon, and the tube was sealed behind a blast shield before placing in a pre-heated oil bath at 88^{o}C. The reaction was left to stir overnight, then was filtered through a pad of celite (1:1 Hexanes : Ethyl Acetate), and concentrated to give a brown oil (36 mg). The crude mixture was purified by flash column chromatography (9:1 Hexanes : Ethyl Acetate) to provide **159** as a slightly yellow oil (9 mg, 0.026 mmol, 41%).

R_f = 0.76 (Hexanes: Ethyl acetate, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.28 (m, 5H), 6.29 (dd, *J* = 10.0, 2.9 Hz, 1H), 5.74-5.63 (m, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 4.52 (s, 2H), 3.53 (t, *J* = 7.2, 2H), 2.69-2.59 (m, 2H), 2.14-2.04 (m, 1H), 1.88-1.77 (m, 2H), 1.70-1.62 (m, 1H), 1.52-1.32 (m, 5H), 1.28-1.23 (m, 2H), 1.21-1.07 (m, 2H), 0.98 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.3, 128.5, 127.7, 127.5, 126.3, 122.3, 120.5, 78.2, 69.9, 44.6, 39.9, 38.1, 35.5, 34.9, 30.7, 29.9, 29.4, 28.5 ppm.

6. Selected Spectra



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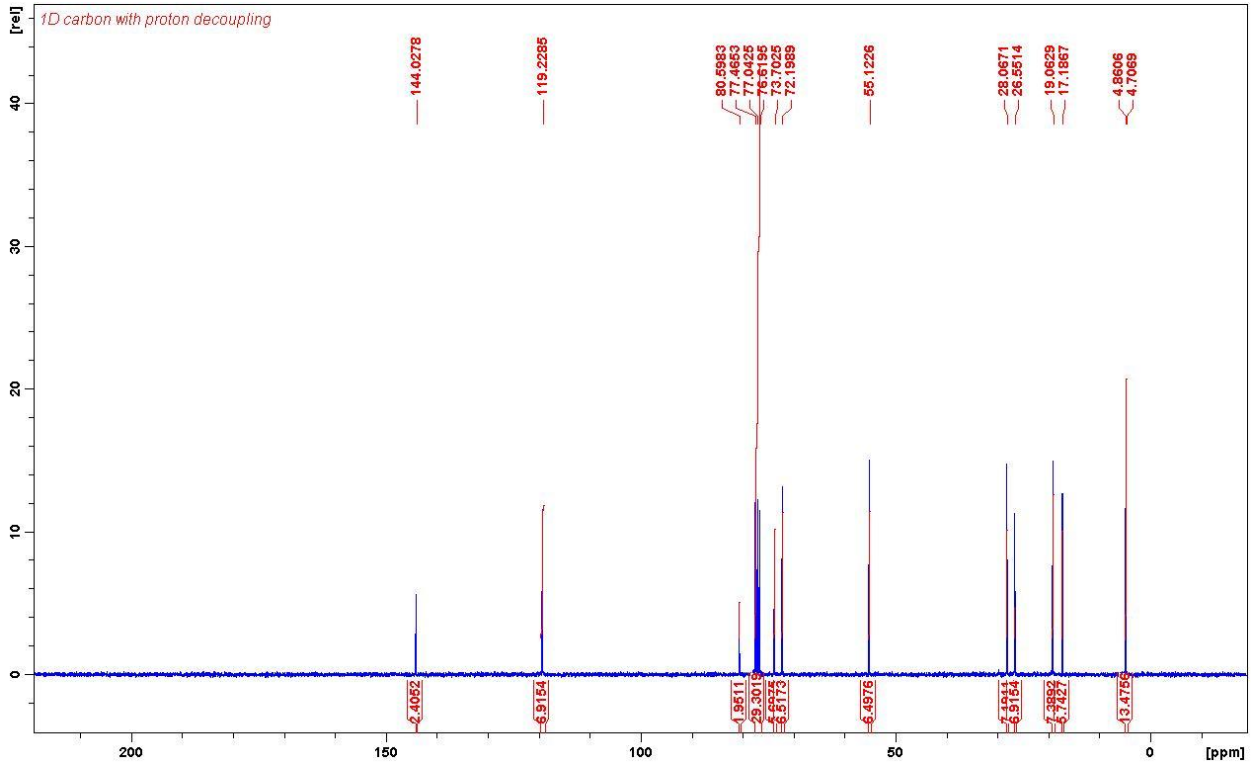
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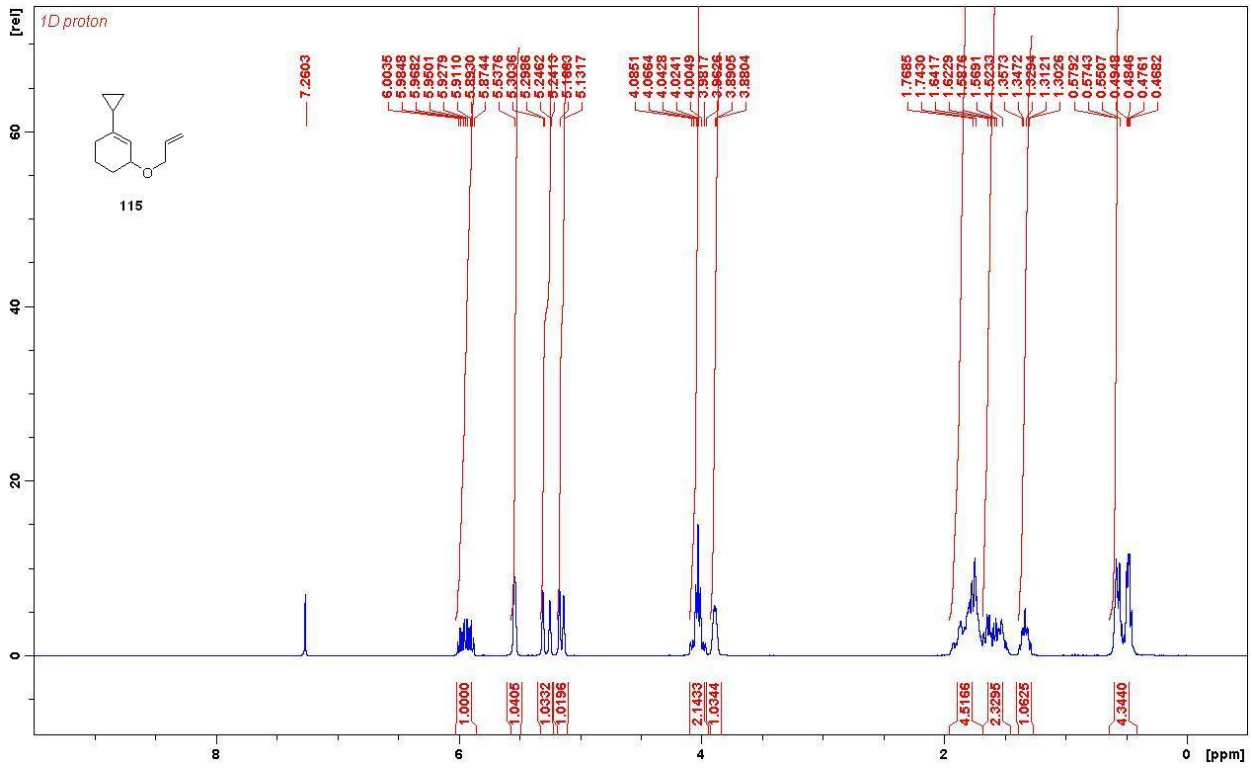
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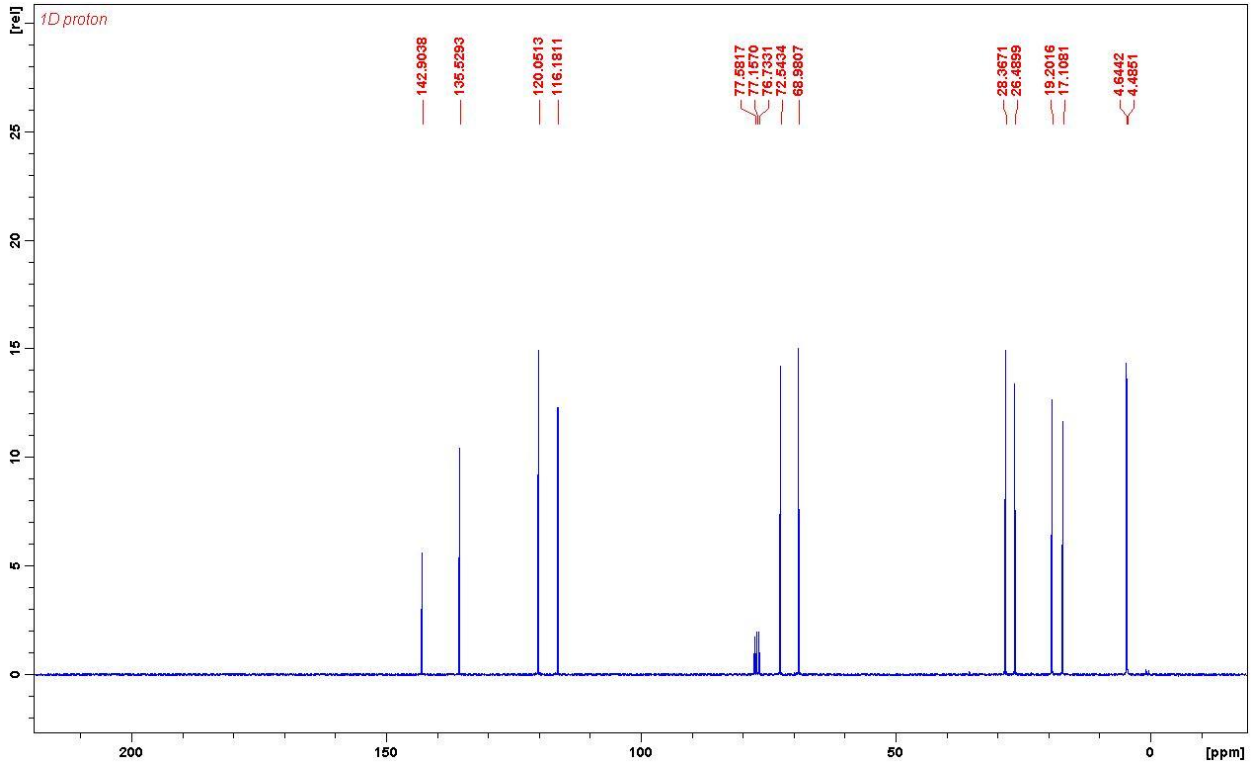
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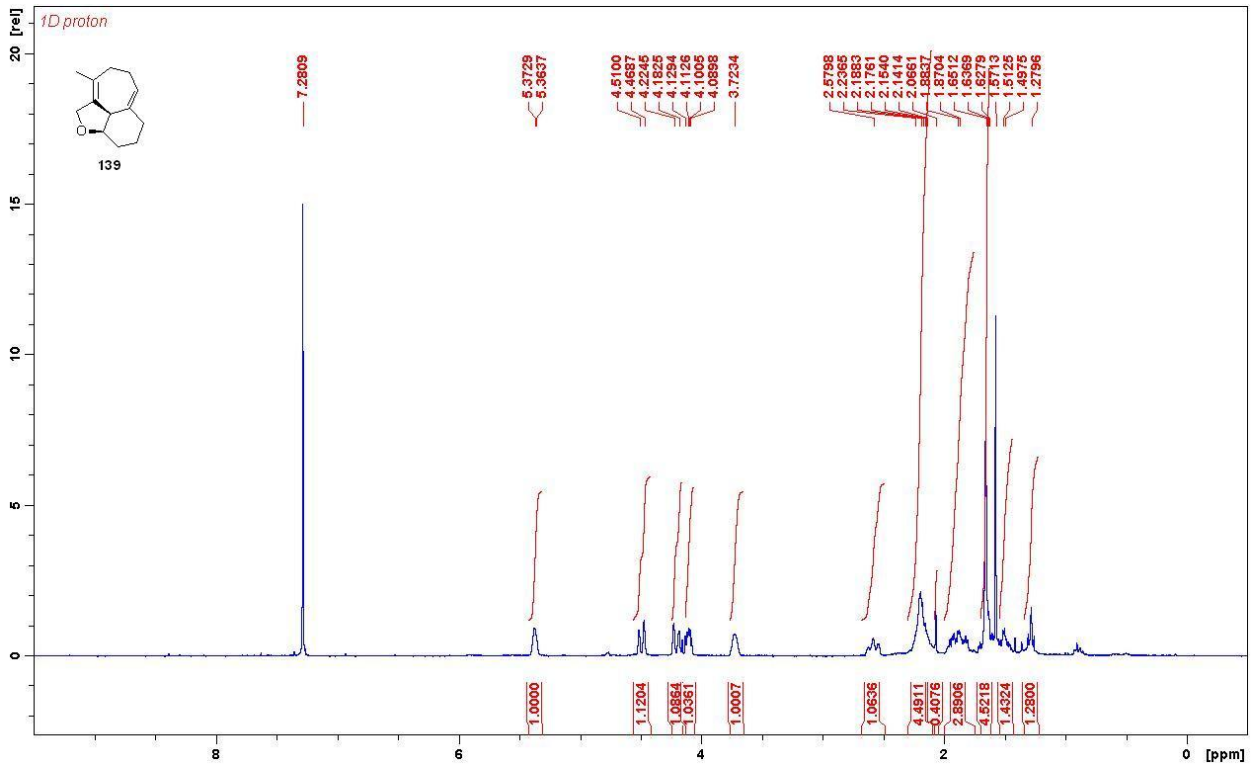
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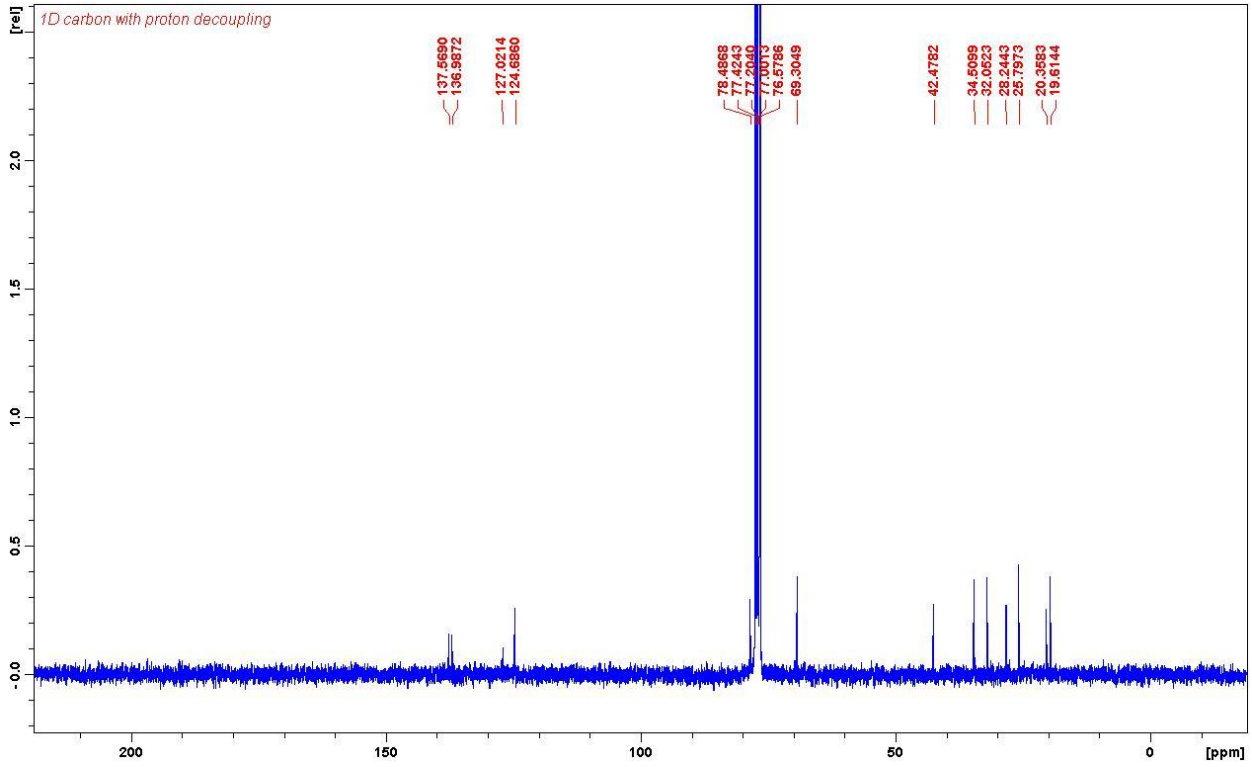
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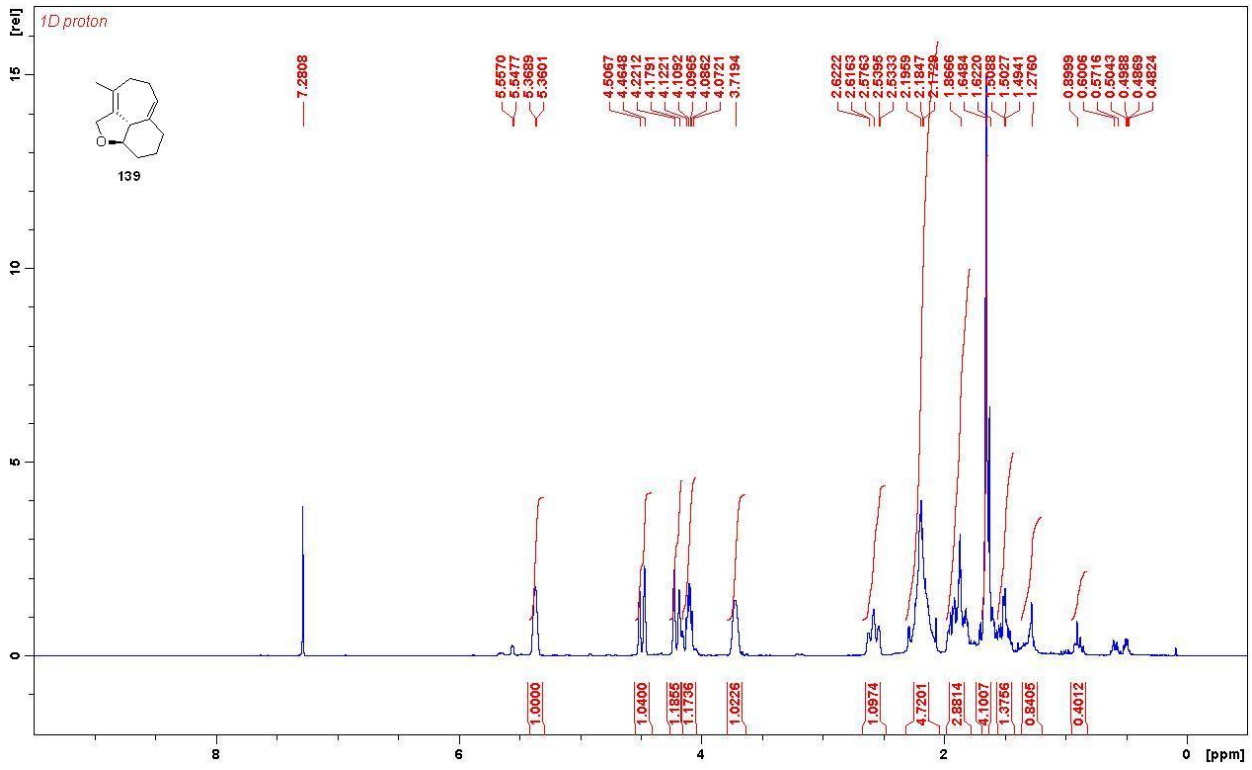
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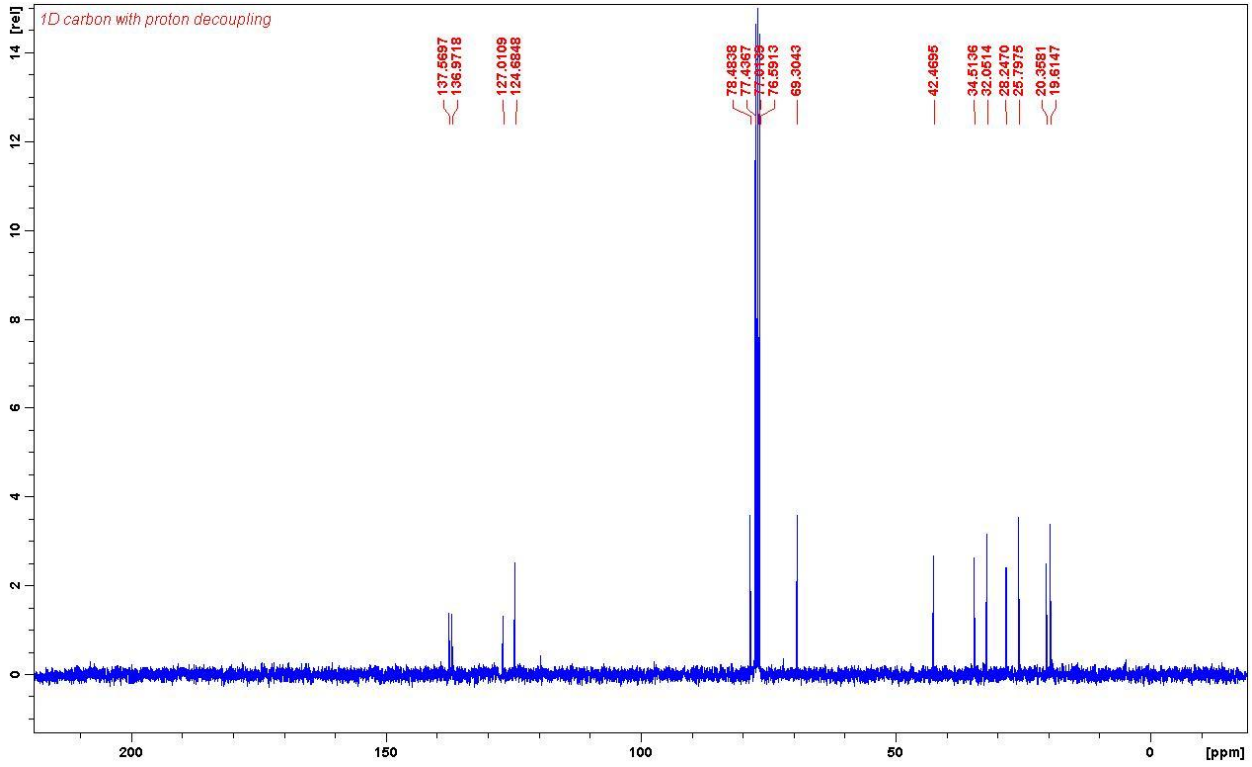
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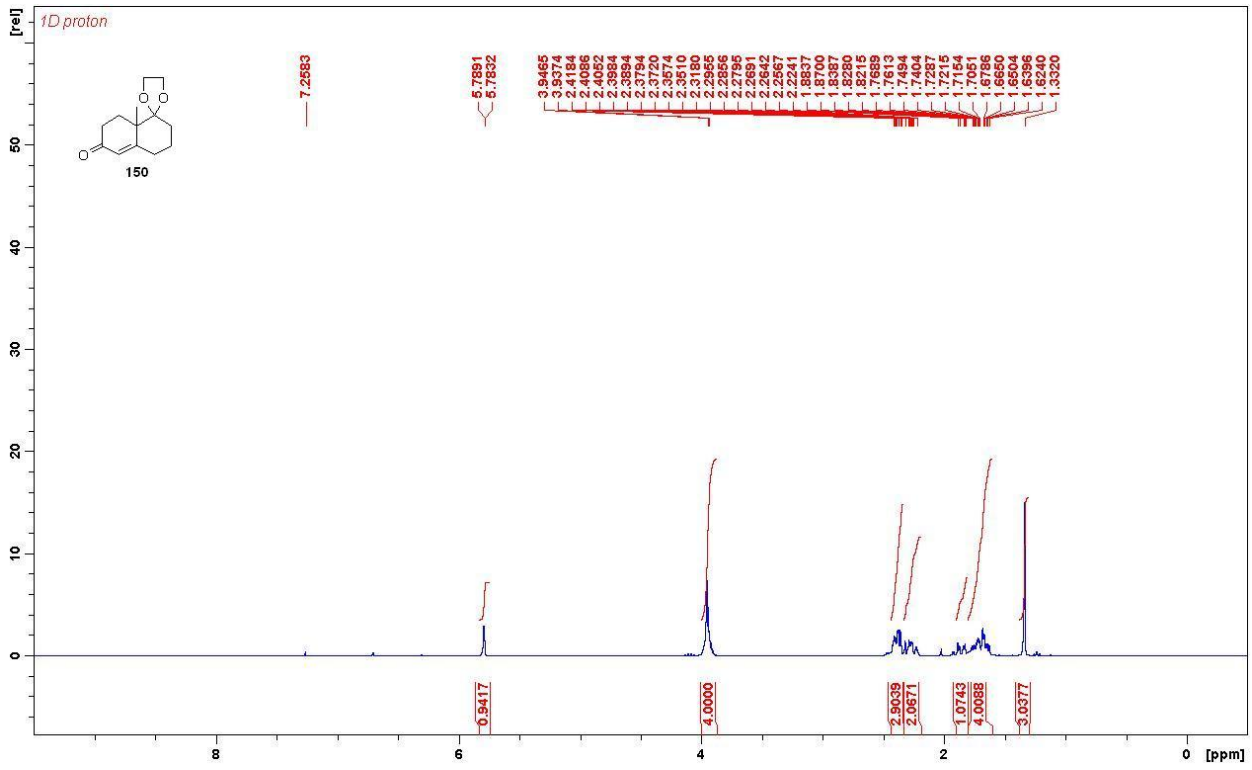
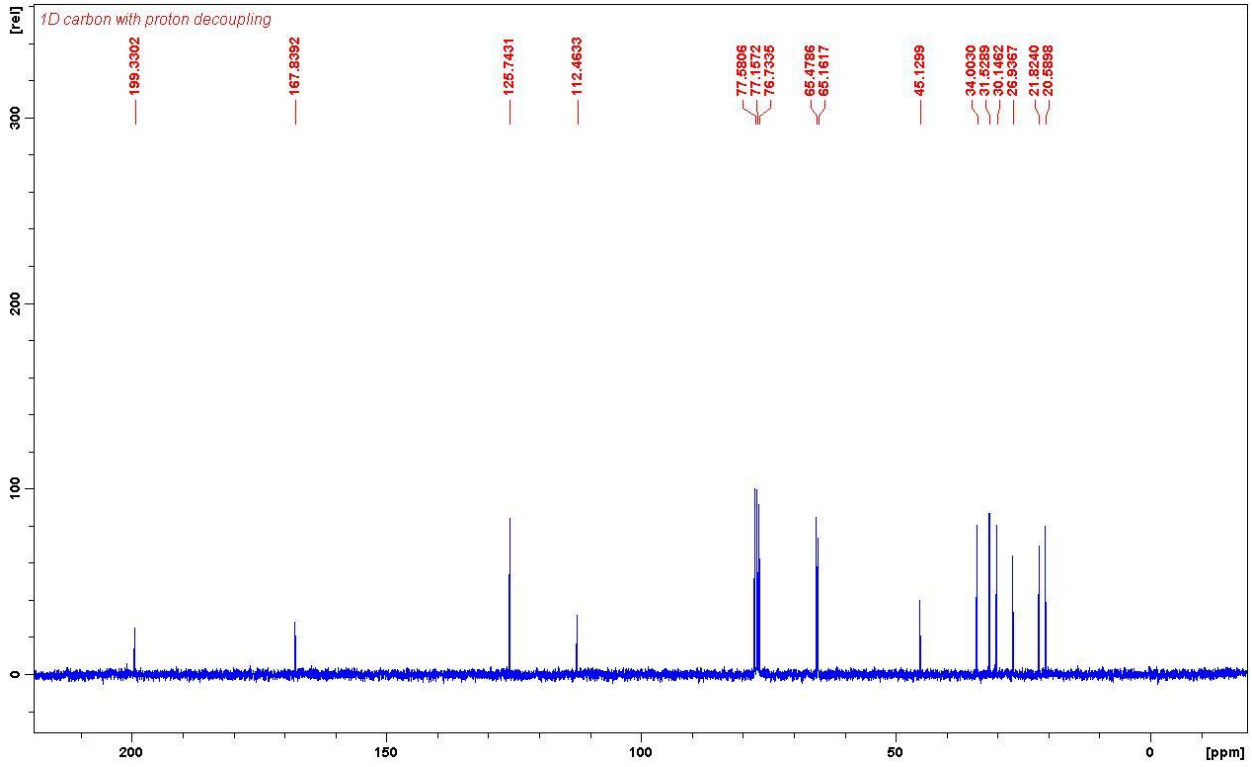
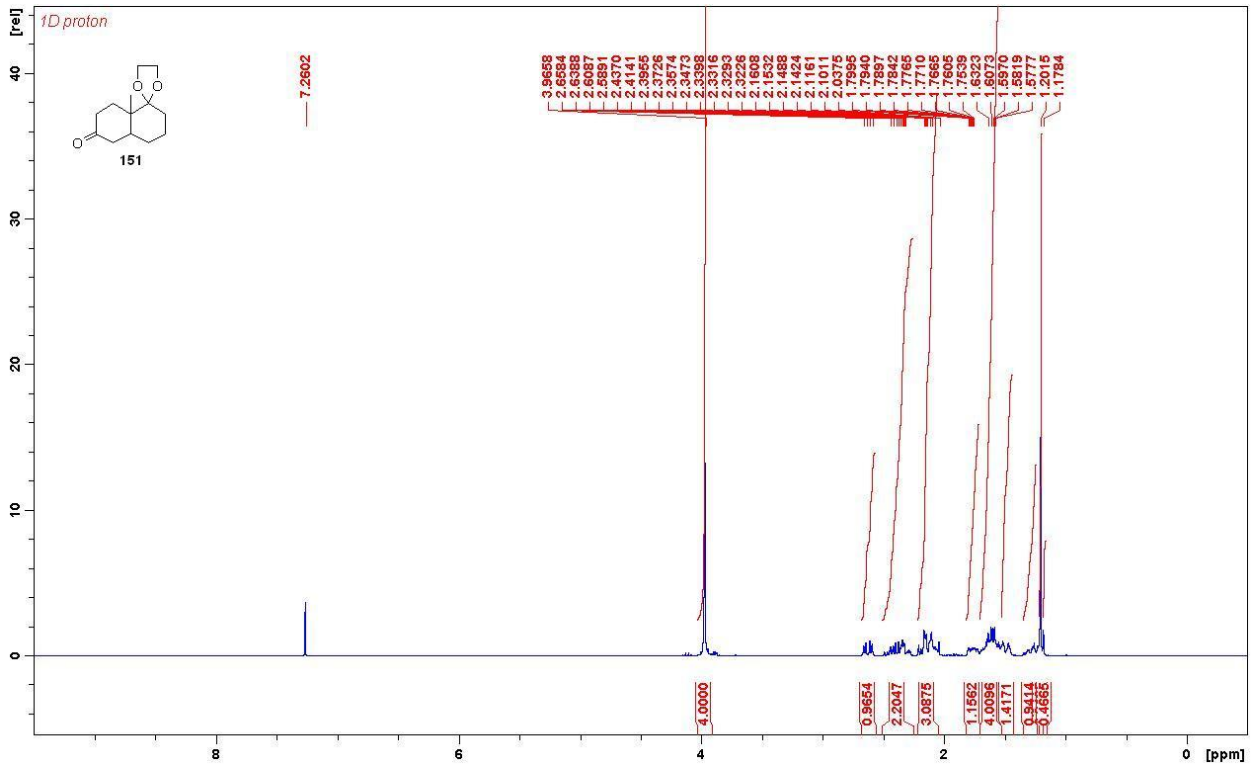
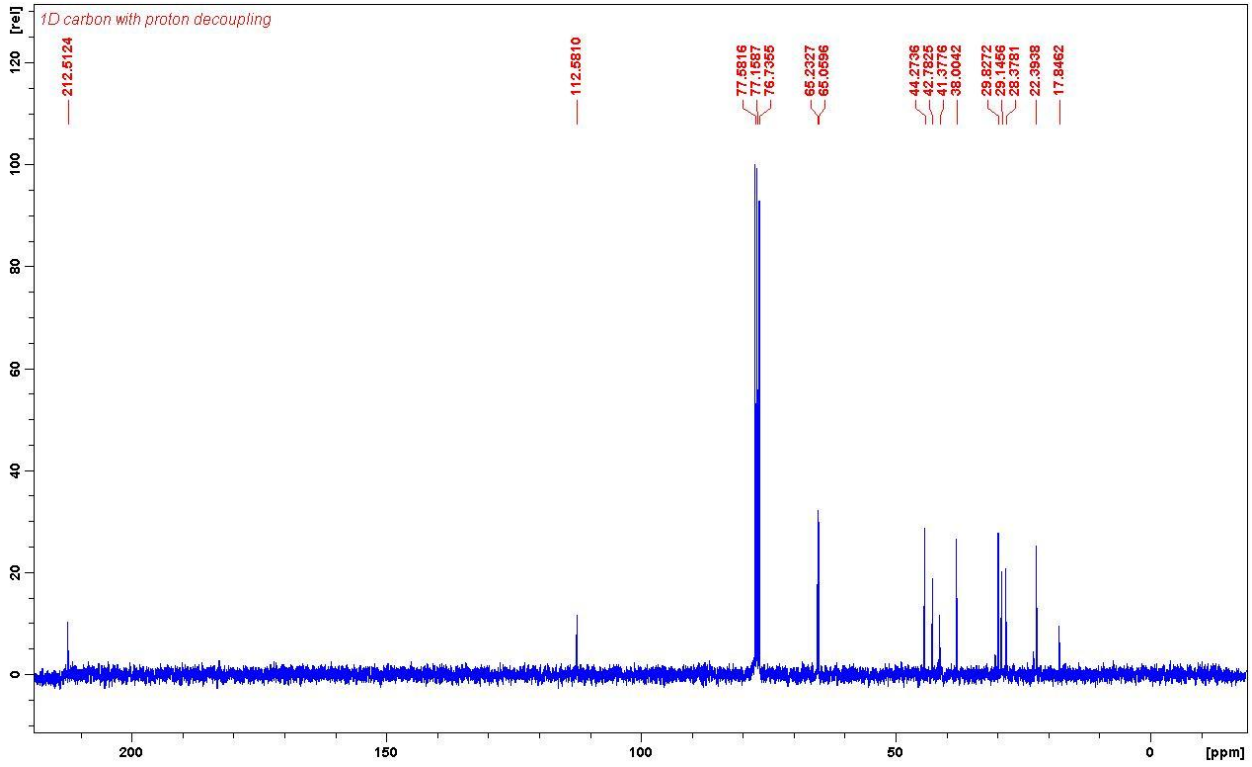
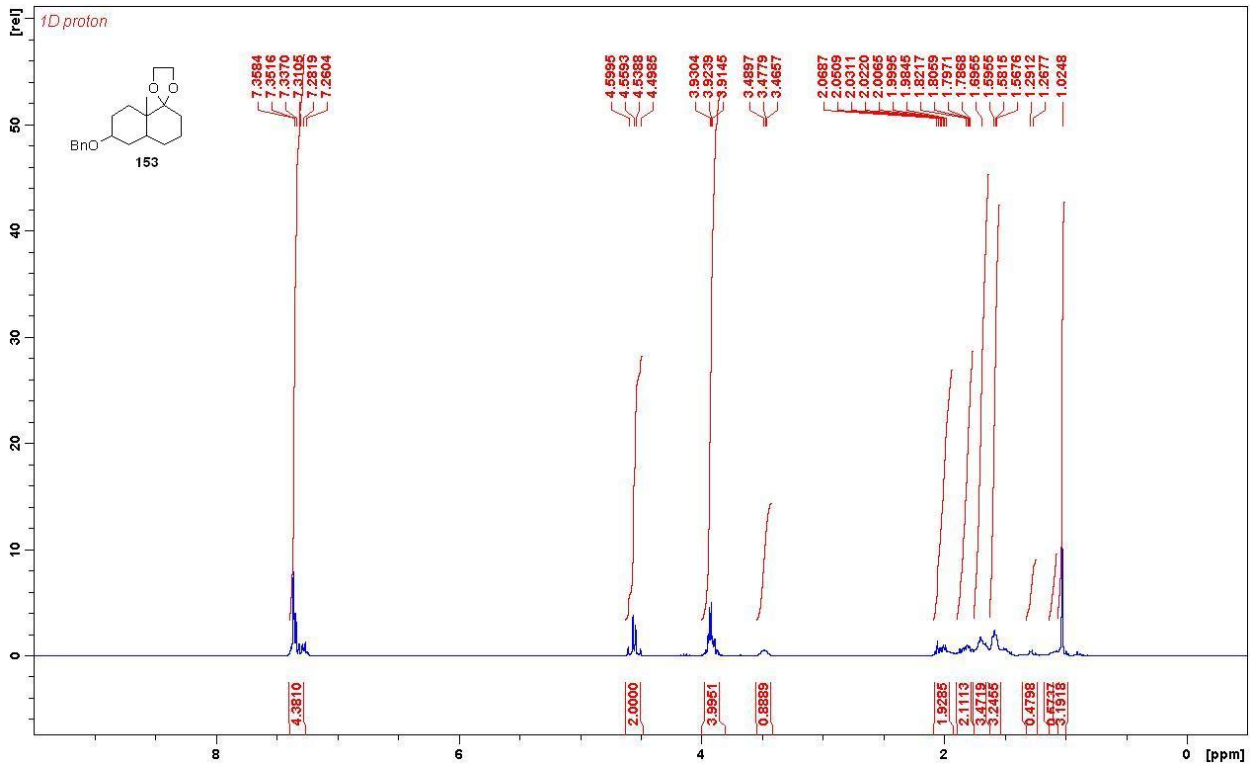
32.0514
28.2470
25.7975
20.3581
19.6147
[rel]
[ppm]

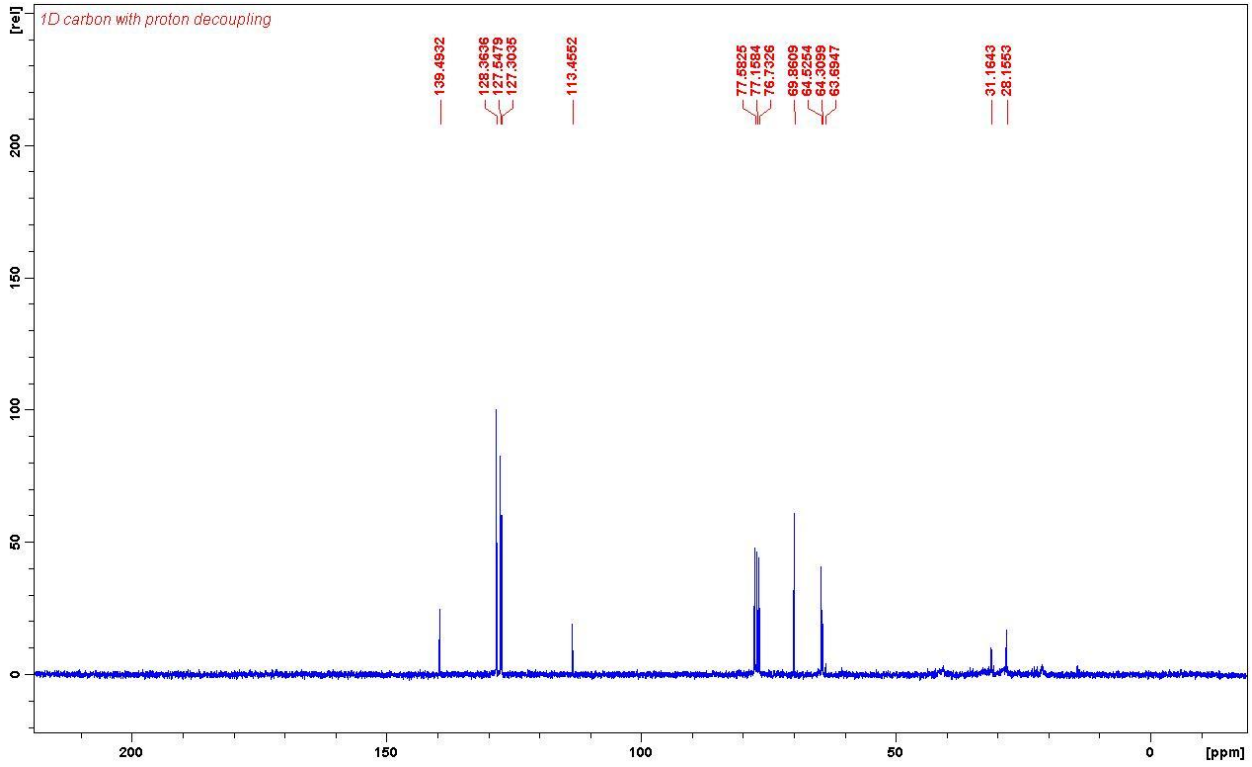

1D proton
[rel]
150
7.2583
5.7891
5.7832
3.9465
3.9374
2.4184
2.4086
2.4052
2.3984
2.3894
2.3794
2.3720
2.3674
2.3610
2.3180
2.2955
2.2795
2.2691
2.2642
2.2567
2.2241
1.8837
1.8700
1.8387
1.8280
1.8215
1.7689
1.7613
1.7494
1.7404
1.7287
1.7215
1.7154
1.7051
1.6786
1.6650
1.6504
1.6396
1.6240
1.3320
0.9417
4.0000
2.9039
2.0671
1.0743
4.0088
3.0377
[ppm]


1D carbon with proton decoupling
[rel]
199.3302
167.8392
125.7431
112.4633
77.5806
77.1572
76.7335
65.4786
65.1617
45.1299
34.0030
31.5289
30.1462
26.9367
21.8240
20.5898
[ppm]


1D proton
151
7.2602
3.9658
2.6584
2.6388
2.6087
2.5891
2.4370
2.4141
2.3965
2.3726
2.3574
2.3473
2.3398
2.3316
2.3293
2.3226
2.1608
2.1532
2.1488
2.1424
2.1161
2.1011
2.0375
1.7995
1.7940
1.7897
1.7842
1.7765
1.7710
1.7685
1.7605
1.7559
1.6323
1.6073
1.5970
1.5819
1.5717
1.2715
1.1784
4.0000
0.9654
2.2047
3.0875
1.1562
4.0096
1.4171
0.9414
0.4665
[rel]
[ppm]


1D carbon with proton decoupling
212.5124
112.5810
77.5816
77.1587
76.7355
65.2327
65.0596
44.2736
42.7825
41.3776
38.0042
29.8272
29.1456
28.3781
22.3938
17.8462
[rel]
[ppm]


1D proton
BnO
153
7.3584
7.3516
7.3370
7.3105
7.2819
7.2604
4.5995
4.5593
4.5388
4.4985
3.9304
3.9239
3.9145
3.4897
3.4779
3.4657
2.0687
2.0609
2.0311
2.0220
2.0065
1.9995
1.9845
1.8217
1.8059
1.7971
1.7868
1.6965
1.5815
1.5616
1.2912
1.2617
1.0248
4.3810
2.0000
3.9951
0.8889
1.9285
2.1113
3.4719
3.2465
0.4798
0.4737
3.1918
[rel]
[ppm]


1D carbon with proton decoupling
139.4932
128.3536
127.5479
127.3035
113.4552
77.6825
77.1584
76.7326
69.8609
64.4254
64.2099
60.8947
31.1643
28.1553
[rel]
[ppm]

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8. Vita

Lee Tyler Bissett was born in Brantford, Ontario, Canada on November 21st, 1985. He graduated from Brantford Collegiate Institute in 2003 and enrolled in the chemistry program at Brock University in 2005, leaving to work in 2006 and returning in 2007, when he was accepted in to Professor Hudlický's research group. Along with Hannes Leisch, he was the awarded best poster presentation at the Latest Trends in Organic Synthesis conference in 2008, published his first paper in 2009, and gave oral presentations at SOUSCC at Brock and WNYACS at Canisius College later that year. Speaking at SOUSCC again in 2010 at Western University, he was awarded the third prize for oral presentations in organic chemistry. He graduated from Brock University with a B.Sc. in Chemistry in 2011 and is currently working towards a Master's degree.